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The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation

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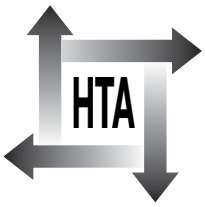

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The research reported in this issue of the journal was commissioned by the HTA Programme as project number 05/38/01. The contractual start date was in October 2005. The draft report began editorial review in January 2007 and was accepted for publication in September 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation

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Objectives: To assess the clinical effectiveness and cost-effectiveness of central venous catheters (CVCs) treated with anti-infective agents in preventing catheter-related bloodstream infection (CRBSI).
Data sources: Major electronic databases were searched from 1985 to August 2005.
Review methods: The systematic clinical and economic reviews were conducted according to accepted procedures. Only full economic evaluations (synthesis of costs and benefits) comparing the use of anti-infective central venous catheters (AI-CVCs) with untreated CVCs or other treated catheters were selected for inclusion in the economic review.
Results: A total of 32 trials met the clinical inclusion criteria. Seven different types of AI-CVC were identified, with the most frequently tested being chlorhexidine and silver sulfadiazine (CHSS) (externally treated), CHSS (externally and internally treated) and minocycline rifampicin (internally and externally treated). In general, the trials were of a poor quality in terms of reported methodology, microbiological relevance and control of confounding variables. The pooled result suggests a statistically significant advantage for AI-CVCs in comparison to standard catheters in reducing CRBSI [odds ratio (OR) 0.45, 95% confidence interval (CI) 0.34 to 0.60, 24 studies, $I^2 = 0\%$, fixed effects]. Analysis by subgroups of catheters demonstrates that antibiotic-treated catheters and catheters treated internally and externally decrease CRBSI rates significantly (OR 0.26, 95% CI 0.15 to 0.46, six studies, $I^2 = 0\%$, fixed effects, and OR 0.43, 95% CI 0.26 to 0.70, nine studies, $I^2 = 0\%$, fixed effects, respectively). Catheters treated only externally demonstrate a wider CI and non-significant effect (OR 0.67, 95% CI 0.43 to 1.06, nine studies, $I^2 = 0\%$, fixed effects). A treatment effect was also found for trials with an average duration of between 5 and 12 days, and for the one study with a mean duration of over 20 days. There was a statistically significant treatment effect for both femoral and jugular insertion sites and for those studies reporting a mix of insertion sites. The treatment effect was not observed in trials using exclusively subclavian insertion sites. Of the four trials that compared treated catheters, one reported a benefit of antibiotic-treated catheters over catheters treated externally with CHSS. All three sensitivity analyses testing for study design differences reported a statistically significant treatment effect. The review was limited owing to the quality of the trials included, marked differences in the definitions and methods of diagnosis of CRBSI, and inconsistent reporting of risk factors and patient population factors. Furthermore, two-thirds of trials were commercially funded. The economic performance (cost-effectiveness and potential cost-savings) of using AI-CVCs to reduce the number of CRBSIs in patients requiring a CVC was also reviewed. Results show that the use of AI-CVCs instead of standard CVCs can lead to a reduction in CRBSIs and decreased medical costs. To complement the reviews, a basic decision-analytic model was constructed to explore a range of possible scenarios for the NHS in England and Wales. Results show that every patient who receives an AI-CVC there is an estimated cost-saving of £138.20. The multivariate sensitivity analyses estimate

potentially large cost-savings, depending on the size of the population, under a wide range of cost and clinical assumptions. However, those considering the purchase of AI-CVCs should ensure that their patient populations and the important characteristics of local clinical practice are indeed similar to those described in this economic evaluation.

Conclusions: Overall, AI-CVCs are clinically effective and relatively inexpensive and therefore their integration into clinical practice can be justified. However, the use of these anti-infective catheters without the appropriate use of other practical care initiatives will have only a limited success on the prevention of CRBSIs. Comparative trials are required to determine which, if any, of the treated catheters is the most effective. Pragmatic research related to the effectiveness of bundles of care that may reduce rates of CRBSI is also warranted.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Anti-infective agent Substance that inhibits the spread of infectious agents. Includes antiseptics, antibiotics, antifungals, antiprotozoans and antivirals.

Antimicrobial agent Substance that inhibits the growth of microorganisms, including bacteria, viruses and fungi.

Catheter-related bloodstream infection A bloodstream infection directly attributable to a central venous catheter.

Central venous catheter (CVC) A catheter passed through a peripheral vein and ending in the thoracic vena cava; it may be used to measure venous pressure or to infuse concentrated solutions.

Colonisation The process by which microorganisms spread into new areas.

Colony-forming units per segment Measure of viable bacterial numbers.

Cuff Band of material around the CVC and tunnelled under the skin.

Cutaneous antisepsis Elimination of microorganisms on the skin.

Endoluminal brush A medical device that allows clinicians to obtain a sample of biofilm from inside a catheter *in situ*.

Endotracheal intubation Placement of a tube into the trachea (windpipe) to maintain an open airway in patients who are unconscious or unable to breathe on their own.

Erythema Redness of the skin.

Femoral vein A major vein sited in the upper part of a thigh.

Flushing Passing of fluid through the CVC.

Guidewire A wire that is inserted into an vessel to guide a catheter to a certain location in the body.

Haemodialysis A procedure for removing metabolic waste products or toxic substances from the bloodstream.

Haemodynamics Forces involved in the circulation of blood.

Jugular vein Any of several large veins of the neck that drain blood from the head.

Lumen A hollow, soft tube that may be separated into two or three individual channels within a catheter.

Maximal sterile barriers Sterile technique used during medical treatment. The definition can vary in the elements, including or excluding sterile gloves, large or standard drapes, head cap, facemask and gown.

Neutropenia An abnormal decrease in the number of neutrophils (white blood cells) in the blood.

Peripheral CVCs A CVC inserted away from the superior vena cava (i.e. in the antecubital fossa).

continued

Glossary *continued*

Plasmapheresis Removal of components of blood plasma from the blood circulation.

Pulsed-field gel electrophoresis A technique used to separate especially long strands of DNA by length to tell differences among samples.

Roll plate method A technique used to measure the number of microorganisms on a catheter segment. The CVC is cultured by rolling on an algar plate.

Seldinger technique Technique of inserting a catheter through the skin as described by Seldinger.

Sonication The process of dispersing, disrupting or inactivating biological materials, such as viruses, by the use of sound-wave energy.

Subclavian vein A vein situated beneath the collarbone.

Total parenteral nutrition Feeding administered through a CVC.

Tunnelled catheter A CVC that is inserted away from the vein and is tunnelled under the skin distal to the vein being accessed.

List of abbreviations

AI-A-CVC	antibiotic-treated CVC
AI-CVC	anti-infective central venous catheter
AI-E-CVC	anti-infective-treated external surface CVC
AI-IE-CVC	anti-infective-treated internal and external surfaces CVC
BSI	bloodstream infection
CE	Conformité Européene
CEA	cost-effectiveness analysis
CFU	colony-forming unit
CG	chlorhexidine gluconate
CHSS	chlorhexidine and silver sulfadiazine
CI	confidence interval
CRBSI	catheter-related bloodstream infection
CRD	Centre for Reviews and Dissemination
CRI	catheter-related infection
CUA	cost–utility analysis
CVC	central venous catheter
DARE	Database of Abstracts of Reviews of Effects
EPIC	Evidence-Based Practice for Infection Prevention
HAI	hospital-acquired infection
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
InCVC	incidence rate of CRBSI with standard CVC
ITT	intention-to-treat
L	local

continued

List of abbreviations *continued*

LOS	length of stay
LRiG	Liverpool Reviews and Implementation Group
MR	minocycline rifampicin
MSB	maximal sterile barrier
NA	not applicable
NAO	National Audit Office
NNT	number needed to treat
NS	not stated
OR	odds ratio
PI	povidone iodine
PICC	peripherally inserted central catheter
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
RRR	relative risk reduction
S	systemic
SA	sensitivity analysis
SD	standard deviation
TPN	total parenteral nutrition

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Central venous catheters (CVCs) include a variety of vascular access devices with a wide range of clinical applications. Although CVCs have had a profound impact on the range and quality of care offered to patients in both hospital and domiciliary settings, their use is also associated with a variety of complications, most notably infection. Such infections may develop in the soft tissues, or be introduced directly through the lumen of the CVC into the bloodstream. The morbidity and mortality associated with these infections have an impact on both the patient and the healthcare system.

Previous reviews have indicated that there may be a clinical benefit of using anti-infective central venous catheters (AI-CVCs) to reduce the complication of catheter-related bloodstream infection (CRBSI). New trial data are available and this review was conducted to integrate these data.

Objectives

The objectives of this report were to assess the clinical effectiveness and cost-effectiveness of CVCs treated with anti-infective agents in preventing CRBSIs.

Methods

The assessment was carried out according to accepted procedures for conducting and reporting systematic reviews and economic evaluations, including identification of clinical and economic studies, application of inclusion criteria, quality assessment of included studies, and data extraction and analysis.

Searching

Evidence on clinical effects and cost-effectiveness of AI-CVCs was identified using a comprehensive search strategy of bibliographic databases (including the Cochrane Library, EMBASE and MEDLINE), as well as checking of reference lists in identified studies. The database searches covered the period from 1985 to August 2005.

Inclusion criteria

The assessment was restricted to published papers of randomised controlled trials testing the clinical effectiveness of AI-CVCs. The relevant comparators were untreated CVCs or other treated catheters.

Clinical outcomes had to include at least a measure of CRBSI, colonisation or clinical signs and symptoms of CRBSI.

Economic evaluation

Only full economic evaluations (synthesis of costs and benefits) comparing the use of AI-CVCs with untreated CVCs or other treated catheters were selected for inclusion in the review.

As part of the study, the economic performance (cost-effectiveness and potential cost-savings) of using AI-CVCs to reduce the number of CRBSIs in patients requiring a CVC was estimated. A basic decision-analytic model was constructed to explore a range of possible scenarios for the NHS in England and Wales.

Results

Clinical review findings

A total of 32 trials met the clinical inclusion criteria. Owing to the diversity of definitions of CRBSI and colonisation, an outcome categorisation system was developed to differentiate among the various microbiological methods and criteria used in the different definitions.

Seven different types of AI-CVC were identified, with the most frequently tested being chlorhexidine and silver sulfadiazine (CHSS) (externally treated), CHSS (externally and internally treated) and minocycline rifampicin (internally and externally treated).

In general, the trials were of a poor quality in terms of reported methodology (e.g. method of randomisation and blinding), microbiological relevance (reporting of colonisation and not CRBSI) and control of confounding variables (patient characteristics).

The pooled result suggests a statistically significant advantage for AI-CVCs in comparison to standard catheters in reducing CRBSI [odds ratio (OR) 0.45, 95% confidence interval (CI) 0.34 to 0.60, 24 studies, I^2 = 0%, fixed effects].

Analysis by subgroups of catheters demonstrates that antibiotic-treated catheters and catheters treated internally and externally decrease CRBSI rates significantly (OR 0.26, 95% CI 0.15 to 0.46, six studies, I^2 = 0%, fixed effects, and OR 0.43, 95% CI 0.26 to 0.70, nine studies, I^2 = 0%, fixed effects, respectively). Catheters treated only externally demonstrate a wider confidence interval and non-significant effect (OR 0.67, 95% CI 0.43 to 1.06, nine studies, I^2 = 0%, fixed effects).

When the duration of insertion was investigated, an average duration of between 13 and 20 days did not result in a statistically significant treatment effect. However, for trials with an average duration of between 5 and 12 days, and for the one study that had a mean duration of more than 20 days, there was a statistically significant treatment effect.

The overall treatment effect was observed for both femoral and jugular insertion sites and for those studies reporting a mix of insertion sites. The treatment effect was not observed in trials using exclusively subclavian insertion sites.

The non-significant findings related to duration and site need to be viewed with caution as the results may be more closely related to overall rates of infection or the type of AI-CVC.

Four trials compared treated catheters. One of these reported a benefit of antibiotic-treated catheters over catheters treated externally with CHSS.

Three sensitivity analyses testing for study design differences were also conducted: analysis by person or catheter, blinding and randomisation. All reported a statistically significant treatment effect.

The review is limited owing to the quality of the trials included, marked differences in the definitions and methods of diagnosis of CRBSI, and inconsistent reporting of risk factors and patient population factors. Furthermore, two-thirds of trials were commercially funded. Such limitations mean that local decisions as to whether or not to adopt AI-CVCs for the prevention of CRBSIs require a clear understanding of the evidence-based reviews and guideline recommendations as well as knowledge of local clinical practice and infection rates.

Economic review findings

Four economic evaluations met inclusion criteria for the review. Three articles were full papers; one was published as a letter. Overall, the quality of the three full economic evaluation papers was high. All of the authors adequately described the research question and comprehensively described the relevant comparators. Only two papers provided the reader with enough information to recalculate and therefore verify the size of the incremental cost-effectiveness ratios (ICERs). The authors all agree that, from a health service perspective, the use of CVCs to prevent CRBSIs is a cost-effective option compared with the use of standard CVCs when used in high-risk populations, and that use of these novel technologies leads to better patient outcomes and reduced costs.

The results from 16 partial economics evaluations are presented. These papers investigated a range of measures to reduce bloodstream infections and CRBSIs and reported associated cost-savings. All but one of the studies explicitly agrees that there are substantial monetary savings to be generated from successfully reducing the number of bloodstream infections. As partial analyses, these papers did not meet the inclusion criteria for the review, but data were used to inform the decision-analytic model.

Economic evaluation

Results show that the use of AI-CVCs instead of standard CVCs can lead to a reduction in CRBSIs and decreased medical costs. Using the constructed decision-analytic model, the incremental cost per patient was estimated to be equal to –£138.20; that is, for every patient who receives an AI-CVC, there is an estimated cost-saving of £138.20. The results of a series of multivariate sensitivity analyses reveal that estimates of potentially large cost-savings, depending on the size of the population, may be anticipated under a wide range of cost and clinical assumptions. However, when considering the purchase of AI-CVCs, decision-makers in the NHS should ensure that their patient populations and the important characteristics of local clinical practice are indeed similar to those described in this economic evaluation.

Conclusions

The use of AI-CVCs reduces the rates of CRBSI for durations of between 5 and 12 days and greater than 20 days when CVCs are inserted in

the femoral or jugular veins. Studies report the best clinical effect when CVCs are treated with minocycline rifampicin or internally and externally treated with silver or CHSS. Further evidence is needed to confirm or refute the benefits of externally treated catheters, most notably the catheters treated with CHSS.

Further evidence is required to test whether AI-CVCs reduce CRBSI for durations of between 13 and 20 days, for CVCs inserted into the subclavian vein and comparing catheters with different treatments.

Current published evidence suggests that AI-CVCs are cost-effective for high-risk patients compared with standard CVCs. However, given the paucity of the economic evidence available, the results of these studies must be interpreted carefully. A simple decision model estimated ICERs for a range of different assumptions and demonstrated that all reasonable scenarios show AI-CVCs to be dominant; that is, in terms of cost-effectiveness, they are cheaper and more effective.

However, the limitations of this review should be recognised. Local decisions as to whether or not to adopt AI-CVCs for the prevention of CRBSIs require a clear understanding of the evidence-based reviews and guideline recommendations as well as knowledge of local clinical practice and infection rates.

Overall, AI-CVCs are clinically effective and relatively inexpensive and therefore their integration into standard care can be justified. However, the use of these anti-infective catheters without the appropriate use of other practical care initiatives will have only a limited effect on the prevention of CRBSIs.

Recommendations for further research

It has been estimated that, to take account of all relevant clinical parameters, including mortality, related to the effectiveness of AI-CVCs, a single clinical trial would have to include around 10,000 patients in each study arm. It is highly unlikely that such a trial will ever be funded.

Comparative trials are required to determine which, if any, of the treated catheters is the most effective.

This review has demonstrated that AI-CVCs can be effective in reducing the number of CRBSIs compared with standard CVCs. Results of the included studies also indicate that rates of CRBSI can be minimised when standard CVCs are used. Therefore, recommendations for pragmatic research related to the effectiveness of bundles of care that may be effective in reducing rates of CRBSI are warranted. Such research will require local audit of CRBSI rates as well as the assessment of current care practices to evaluate the clinical effectiveness and cost-effectiveness of implementing a package of care to reduce CRBSI rates.

Chapter 1

Objectives and background

Objectives

The objectives of this research were to establish the clinical effectiveness and cost-effectiveness of central venous catheters (CVCs) treated with anti-infective agents in preventing catheter-related bloodstream infections (CRBSIs).

Background

CVCs include a variety of vascular access devices with a wide range of clinical applications, which include:

- monitoring of haemodynamic status in critically ill patients
- providing fluid replacement therapy
- administering blood products
- delivering intravenous drug therapy (e.g. antibiotics, chemotherapy)
- administering total parenteral nutrition (TPN)
- providing access for haemodialysis and plasmapheresis.

Although CVCs have had a profound impact on the range and quality of care offered to patients in both hospital and domiciliary settings, their use is also associated with a variety of complications, most notably infection. Such infections may develop in the soft tissues (around the CVC insertion site, or in the tunnel between the puncture site in the skin and entry into the vein), or be introduced directly through the lumen of the CVC into the bloodstream. The morbidity and mortality associated with these infections impact on both the patient and the healthcare system.

In recent years there has been the commercial development of CVCs treated with various anti-infective agents, designed to combat infection on and around the CVC. The 2001 Department of Health guideline recommendations[1] relating to the use of these anti-infective-treated CVCs were based on a variety of review and trial evidence, including one meta-analysis (1999) that combined data from 11 studies published between 1994 and 1998.[2] By 2003 five further systematic reviews[3–7] had been published, four using meta-analysis. Three of the reviews commented on the need for further trials to address a variety of methodological flaws identified by the research.[3,5,7] A summary of these reviews is presented in Appendix 1. By July 2005 a further 11 trials had been published.[8–18] This review was commissioned to determine the clinical effectiveness and cost-effectiveness of CVCs treated with anti-infective agents (AI-CVCs).

Description of the health problem

The use of CVCs has increased over time, bringing with it an increase in the incidence of adverse events, notably CRBSIs. CRBSIs are systemic blood infections (bacteraemia) directly attributable to a CVC. A precursor to bloodstream infection (BSI) is colonisation either of the insertion site or of the CVC hub. From these sites the organisms reach the CVC tip along either the external or the internal surface of the CVC. Colonisation of the CVC tip may then lead to bloodstream infection.

CRBSI is associated with increased morbidity, mortality and duration of hospital stay.[19] From the patient perspective, there may be soft-tissue pain, systemic symptoms such as pyrexia (prompting investigations including blood tests and X-rays), a need to replace an infected CVC, antibiotic treatment, prolonged hospitalisation and (infrequently) death.

Epidemiology

CVC use

Data related to the use of CVCs are not routinely collected. The most up-to-date information in 1994 estimated that across the NHS over 200,000 CVCs were inserted in adult patients each year.[20] As the average cost of insertion was estimated to be approximately £500, the annual direct cost to the NHS of CVC insertions was conservatively estimated to exceed £100 million.[21] However, recent contacts with suppliers of CVCs in the UK would suggest that at least 238,500 CVCs were purchased in 2004/05.

CRBSI

UK data on the acquisition of CRBSIs are not systematically collected. In 1991 approximately

4000 cases of CRBSI were reported by the Communicable Disease Surveillance Centre (CDSC) of the Public Health Laboratory Service, UK.[22] In 1994, information from the Department of Health indicated that as many as 6000 patients may have been affected each year[1] and that attributable mortality from such infections may have been as high as 10–25%.[2] If, as reported by Elliott and colleagues,[20] 200,000 CVCs were inserted annually in the NHS, then this Department of Health figure is supported by Fletcher,[23] who stated that CRBSIs occur in approximately 3% of catheterisations.

In the USA, up to 5 million CVCs are inserted each year and approximately 200,000 (4%) of patients reportedly develop a CRBSI; the number of deaths attributable to CRBSI has been estimated at 25,000 (12.5%), equating to 0.5% of CVC insertions.[24]

Despite the scale of the problem having been recognised for over a decade, only relatively recently has prevention of these infective complications become systematically targeted. National guidance on evidence-based clinical standards for preventing healthcare-associated infections (EPIC 2001 and 2006)[1,25] and practical guidance on implementing these (Royal College of Nursing)[26] have been developed and published.

Risk factors

The risk factors for CRBSI fall into two categories: catheter care and patient characteristics (*Table 1*).

Catheter care

For a CVC to become infected the microorganisms need to be present and infect either the insertion site or the CVC itself. The risk of catheter-related infection may therefore be reduced by preventing contamination of the CVC. The factors related to reducing contamination are shown in *Table 1* and cover all aspects of CVC care.

The Department of Health issued national guidance on Evidence-Based Practice for Infection Prevention (EPIC) to NHS Trusts in England and Wales in 2001.[1] These guidelines examined the evidence of the effectiveness of practices aimed at reducing catheter-related infections. From the evidence they made recommendations related to the choice of CVC, site of insertion, use of optimum aseptic techniques at insertion and during the care of the CVC, replacement of CVCs and the use of antibiotics.

These guidelines were updated and published in 2006. The update includes 47 recommendations that are categorised as education of patients, their carers and healthcare personnel, general asepsis, CVC site care and general principles for CVC management (see Appendix 2).

Patient characteristics

Although the risks of CVC contamination can be minimised by good CVC care, there are two categories of patients who are (1) more susceptible to CRBSIs or (2) prone to more severe CRBSIs owing to their reduced ability to fight infection.

Consequences of CRBSI

There is no universally accepted clinical pathway for the management of a CRBSI. In general, management of a CRBSI includes removal and reinsertion of the CVC, oral or intravenous antibiotics or antibiotic line lock.[28] An economic consequence of CRBSI is that a prolonged length of stay in hospital on a general ward and/or intensive care (depending on the patient's health state) will be required. Detailed management of a

TABLE 1 *Risk factors associated with CVC-related infections*

Catheter care	Patient characteristics
Choice of CVC	**A (more likely to suffer CRBSI)**
Number of CVC lumens	Loss of skin integrity
Insertion site	Presence of local or distant infection
Method of insertion	**B (prone to more severe CRBSI)**
Experience of the person inserting the CVC	Shock
Contaminated skin solutions	Susceptibility to infection (neutropenia, immunosuppression)
Infusate apparatus	Prior antibiotic therapy
Care of site	Severity of underlying illness
Frequent manipulations	Malignancy
Prolonged catheterisation	

Adapted from Civetta *et al*. (1996)[27] and Pratt *et al*. (2007).[25]

CRBSI will depend on the health status of the patient, the need for central venous access and the pathogen causing the CRBSI.

CVCs treated with anti-infective agents

In recent years there have been significant developments in the design of new CVCs aimed at reducing the risk of CRBSI. The majority of these innovations use an anti-infective agent, either an antiseptic or antibiotic, to coat either the internal or external surface of a CVC, or both. Commercially available AI-CVCs that have been studied in clinical trials are shown in *Table 2*. To prevent both internal and external contamination of CVCs a second generation of commercially available AI-CVCs that are coated on both surfaces has been introduced.

This review distinguishes between AI-CVCs coated on the external surface only (AI-E-CVCs), CVCs coated both internally and externally (AI-IE-CVC) and CVCs treated with antibiotics that are all treated internally and externally (AI-A-CVC).

Concerns regarding the use of AI-CVCs

Recent debate regarding the use of AI-CVCs has focused on the possibility of hypersensitivity. Some patients may experience a hypersensitivity reaction to the use of silver or CHSS-coated CVCs. Hypersensitivity reactions to silver and CHSS following CVC insertion appear to be rare, with fewer than 20 cases reported worldwide.[29,30] Nonetheless, others have estimated that both the costs to the patient and economic costs associated with such hypersensitivity reactions could be significant.[31]

In addition, the use of AI-A-CVCs has led to concern that this will lead to the emergence of antibiotic-resistant organisms. However, further clinical investigations are necessary before it can be stated with any certainty that these AI-A-CVCs do or do not predispose to the development of resistance.[32]

Diagnosis of CRBSI

The diagnosis of CRBSI is controversial. There are several methods of varying certainty, as discussed below. Inconsistent use of terms (e.g. catheter-related bacteraemia, catheter-related sepsis) further confuses the issue.[33] Diagnosis of CRBSI should include:

- clinical symptoms and signs, which may be local inflammation (pain, erythema, purulent discharge) or systemic symptoms such as fever and rigors
- microbiological confirmation and typing in the laboratory.

Microbiological methods

Accurate diagnosis of CRBSI requires that both colonisation of the CVC be ascertained in the laboratory using standardised methodologies and end-points, and an identical organism be isolated from the bloodstream using blood cultures taken from a peripheral vein to demonstrate haematogenous spread of the organism.[25]

The prevalent methods and criteria used for the diagnosis of CVC colonisation on the external and internal surfaces of CVCs are summarised in *Table 3*.[34]

TABLE 2 *Types of AI-CVC and the surfaces treated for each*

Category	Treatment	Surface treated	
		Extraluminal	Intraluminal
AI-E-CVC (first generation)	CHSS	✓	×
	Silver	✓	×
	Silver, carbon and platinum	✓	×
AI-IE-CVC (second generation)	Silver impregnated	✓	✓
	Benzalkonium chloride impregnated	✓	✓
	Silver impregnated cuff	✓	✓
	CHSS Plus	✓	✓
AI-A-CVC	Minocycline rifampin	✓	✓
	Miconazole and rifampicin	✓	✓

CHSS, chlorhexidine and silver sulfadiazine.

TABLE 3 *Microbiological methods for diagnosis of CVC colonisation*

Method	End-point	External surface	Internal surface
Roll plate method[35,36]	>15 CFU per segment	✓	×
Luminal flushing[37]	>1000 CFU per 1 ml	×	✓
Endoluminal brushing	>1000 CFU per 1 ml	×	✓
Sonication	>1000 CFU per 1 ml	✓	✓

CFU, colony-forming unit.

- *roll plate method*: the catheter segment is rolled across the surface of an agar plate and CFUs are counted after overnight incubation.
- *flushing*: the lumen of the catheter segment is flushed with broth, followed by counting the CFUs that grow from the washout after 24 hours.
- *endoluminal brushing*: a sterile endoluminal brush is introduced a defined distance into the catheter, removed and then cultured overnight. This method has been validated, but is not in common use.
- *sonication*: the whole of the catheter segment is sonicated in broth to release organisms attached to both internal and external surfaces, followed by counting the CFUs that have been released.

Until recently it has been standard practice to regard organisms isolated from the CVC and the bloodstream as identical if they are of the same species and morphological appearance, and have the same antibiotic sensitivity pattern. Recent research studies, however, using molecular fingerprinting techniques, have revealed that apparently identical isolates may in fact be different on as many as 20% of occasions.[38]

One other issue is the problem of neutralising residual antimicrobial activity on the catheter which might suppress the isolation of colonising bacteria in the laboratory. This is accepted as good practice in many areas of microbiological evaluation of anti-infective efficacy.

Surrogate markers

As CRBSIs are relatively rare, surrogate end-points are frequently used in clinical trials. Surrogate markers of a CRBSI include colonisation of the insertion site and catheter tip at removal. Since there is a strong correlation between the rates of catheter tip colonisation and CRBSI ($r = 0.69$, $r^2 = 0.48$, $p < 0.001$)[39] many studies measure and report the colonisation rates of CVCs. However, only a minority of colonised CVCs result in CRBSI.

In addition, a CVC tip may become contaminated during removal while being withdrawn through a colonised insertion site. These organisms may not have been present on the catheter tip in the bloodstream; therefore, measures of catheter tip colonisation are not necessarily accurate markers of CRBSI.

Economic considerations

The benefits of preventing a CRBSI are numerous. If a CRBSI can be avoided then the patient will spend a shorter time in hospital, require fewer medications and be in better health.

As the demand for CVCs continues to increase, so too does the number of CRBSIs. As a result, it is estimated that substantial resources are spent treating CRBSIs every year in the UK NHS. This is attributable to increased patient length of stay (LOS) in hospital and increased use of scarce healthcare resources due to the worsening severity of the patient's underlying condition.[40] It is argued that reducing the number of CRBSIs may therefore lead to substantial monetary savings for hospitals throughout the NHS.

CRBSIs make up a proportion of hospital-acquired infections (HAIs). Recent estimates of the cost of HAIs are available from the National Audit Office (NAO). In 2000, the NAO reported that hospital-acquired infections were each year costing the NHS around £1000 million and resulting in at least 5000 deaths.[41] Plowman and colleagues[42] agree with this figure as they estimated that in 1994/95 the national burden of HAI was approximately £930 million. Unfortunately, no figure exists to quantify the proportion of HAIs which are CRBSIs for the NHS in England and Wales. To date, it appears that no UK studies have calculated the savings directly associated with CRBSIs in the UK NHS.

In summary, although the use of CVCs accounts for the vast majority of hospital-acquired BSI, the rates of CRBSIs in patients in community and

TABLE 4 *Conclusions from six reviews*

Study	Reduce CRBSI	Notes
Veenstra, 1999[2]	Yes	40% reduction applicable if patient population is consistent, high risk, short-term use of multilumen CVC
Marin, 2000[4]	Yes	Also conclude that they are also cost-effective
Walder, 2002[7]	Yes	Short-term effective (< 1 week). Lack of evidence for longer term. No evidence for cuffs
Pai, 2001[6]	No meta-analysis	Based on Veenstra (1999),[2] concluded that CHSS effective in short term and AI-CVC treated with MR reduce CRBSI as all trials were significant
		MR superior to CHSS (in short term)
McConnell, 2003[5]	No meta-analysis	Too many methodological flaws in trials to be confident of any results
Gastmeier, 2003[3]	Yes, but only in the short term	Inconclusive
		Too few trials on catheters impregnated/coated with anti-infective agents other than CHSS
		CHSS reduces CRBSI if short-term catheterisation (<8 days) was included
		Methodological flaws of trials

MR, minocycline rifampicin.

primary healthcare settings in England are unknown.[43] As a result, the true cost of CRBSIs to the NHS in England and Wales cannot be determined with accuracy.

Previous reviews of effectiveness

Six systematic reviews of the clinical effectiveness of AI-CVCs have been published.[2–7] A summary of these reviews is presented in Appendix 1 and the conclusions drawn by each of the reviews are shown in *Table 4*.

Four of the reviews conducted meta-analyses; all four reported a significant reduction in CRBSI when impregnated/coated catheters were used in the short term. All of the reviews mentioned some methodological issues that should be considered. The most recent review was by Gastmeier and colleagues (2003),[3] and although they concluded that AI-CVCs were effective in the short term, information regarding longer term use or the different types of AI-CVCs was inconclusive.

Chapter 2
Methods

Methods for reviewing clinical effectiveness

Search strategy

A comprehensive search strategy was developed and used to interrogate electronic databases for the period from 1985 to August 2005. The search had no language restrictions. Search terms included a combination of index terms (e.g. catheter infection) and free text words (e.g. venous or catheter). Details of the electronic search strategies used and the number of references retrieved for each search are provided in Appendix 3.

Reference lists of retrieved articles and reviews were searched to identify further studies. Companies manufacturing AI-CVCs were contacted for information on ongoing trials or any trials the searches had failed to identify.

All references were exported to EndNote reference database, Version 8 (ISI Research Soft, California, USA).

Inclusion and exclusion criteria

The identified citations were assessed for inclusion through two stages and disagreements were resolved by discussion. In stage 1, two reviewers (JH, RD) independently scanned all the titles and abstracts and identified the potentially relevant articles to be retrieved. In stage 2, full text copies of the selected papers were obtained and each assessed independently by at least two reviewers for inclusion (JH, RD, GS). Details of inclusion and exclusion criteria are presented in *Table 5*.

TABLE 5 *Databases searched and inclusion and exclusion criteria*

	Clinical effectiveness	**Cost-effectiveness**
Electronic databases	MEDLINE (OVID) EMBASE SCI//Web of Science SCI/ISI Proceedings The Cochrane Library	MEDLINE (OVID) SCI/Web of Science SCI/ISI Proceedings The Cochrane Library
Study design	RCT	Full economic evaluations
Population	Patients requiring a central venous catheter	
Interventions	AI-CVCs	
Comparator	Standard CVCs AI-CVCs	
Outcomes	Primary outcome • Catheter-related bloodstream infection Secondary outcomes • Clinical symptoms • Colonisation • Local clinical signs	Catheter-related bloodstream infection avoided Case detected Death Cost-effectiveness ratios Cost per catheter-related bloodstream infection avoided Cost per case detected Cost per death avoided
Exclusion criteria	Non-RCTs AI-CVCs requiring in-house preparation Interim data only	The main source of clinical efficacy data was not explicitly stated No attempt to synthesise costs and benefits was conducted The source was a letter, editorial, review, commentary or methodological paper

RCT, randomised controlled trial.

Quality assessment

Two reviewers (JH, YD) independently evaluated the included studies for methodological quality. This involved methodological assessment for clinical effectiveness based on the Centre for Reviews and Dissemination (CRD), York, Report 4[44] (see Appendix 4). Any discrepancies were resolved through discussion.

Data extraction

Data extraction was carried out independently by two reviewers (JH, KD). Data from each trial relating to trial design and clinical outcomes were extracted using a pretested data extraction form and checked by the second reviewer. Clinical queries were resolved by GS and general queries were resolved by either CG or RD. As part of a parallel project it was necessary to contact a selection of the authors of the included studies. Details of additional data requested and provided are presented in Appendix 5.

Advisory panel

An advisory panel was established to guide the review process. The role of the advisory panel was to answer specific questions as the review progressed and to comment on an early draft of the review including identifying missed or ongoing studies. One of the advisory team (GS) provided clinical expertise throughout the review and is therefore listed as an author of this report.

Statistical methods

Using Review Manager 4.2[45] reviewer KD conducted, where appropriate, meta-analyses to assess the effectiveness of AI-CVCs in preventing CRBSIs, compared with no anti-infective agents. Studies that compare different anti-infective agents were not combined with studies that use a standard control (no anti-infective agent), but were investigated separately.

Where multiple CRBSI diagnostic methods were reported, the most reliable method was included in the analysis (see the section 'Approach to analyses', p. 30). Results are presented in forest plots with 95% confidence intervals (CIs).

For binary data, Peto's odds ratio (OR) was used, as this has been shown to be the best method where there are low event rates.[46] The odds ratio is approximately equal to the relative risk (RR). This method was used for analysis related to CRBSI, which rarely occurs, while RR was calculated for analysis of colonisation data, as colonisation is a more frequent occurrence.

Meta-analyses are presented for all trials comparing AI-CVCs with standard CVCs and also subgrouped by whether the AI-CVCs were treated with an antibiotic (AI-A-CVC), whether they were coated with an anti-infective extraluminally only (AI-E-CVC) or both intraluminally and extraluminally (AI-IE-CVC).

Heterogeneity was investigated by visually examining the forest plots to see whether the confidence intervals overlap. The χ^2 test[47] using a 5% level of statistical significance and the *I*-squared[48] test with a value of 50% used to indicate moderate levels of heterogeneity were also used. The following subgroups were used to examine heterogeneity: type of treated catheter, different outcome categorisations, duration and insertion site. DerSimonian and Laird's random effects model[49] was used when statistical heterogeneity was detected.

Sensitivity analyses were carried out for methodological quality (randomisation and blinding) and studies analysed by person rather than by CVC. The latter sensitivity analysis had to be considered as studies that included more than one CVC per person needed to analyse the data to allow for the clustering of these catheters within an individual. If the analysis is carried out by CVC without allowing for multiple catheters per person then this may result in confidence interval widths being too narrow and cause inappropriate weighting in the meta-analysis.

Publication bias was investigated using a funnel plot.

Methods for reviewing cost-effectiveness

A comprehensive review of the literature was undertaken to identify all published articles that could provide evidence with regard to the cost-effectiveness of anti-infective-treated CVCs for the prevention of CRBSI.

The search incorporated a number of strategies. Search terms for electronic databases included a combination of index terms (e.g. central venous catheter and infection) and free text words (e.g. venous and infection). No limitation was included on study type or language.

Reference lists of included studies were searched to identify other relevant cost-effectiveness studies. Internet resources were examined for information on cost data.

Identification of cost-effectiveness evidence

The records identified in the electronic searches were assessed for inclusion in two stages. First, two reviewers independently scanned all the titles and abstracts and identified the potentially relevant articles to be retrieved (AB and CM). Any differences in selection choice were discussed between the reviewers and consensus was reached in all cases. Full text reports of these selected papers were then obtained and assessed for inclusion independently by the same reviewers.

Selection of cost-effectiveness evidence

Using explicit, predetermined criteria, two reviewers (AB and CM) independently identified reports for inclusion in the review of published economic evaluations and as a source of cost data to inform the development of the economic model. Any disagreements regarding the inclusion of identified reports for the cost-effectiveness assessment were resolved through discussion. The inclusion/exclusion assessment of each reviewer was recorded on a pretested, standardised form. The inclusion and exclusion criteria used in the selection of cost-effectiveness evaluations are shown in *Table 5*.

Chapter 3

Clinical review

Selection of included studies

As shown in *Figure 1*, the electronic searches identified 871 individual papers. After stage 1 screening, 53 relevant references remained to which the inclusion criteria were applied. Of these, 35 studies met the inclusion criteria. When data quality assessment was conducted it was found that three of these trials[50–52] did not use true randomisation methods and were therefore excluded. One of these trials inserted different CVCs on alternate days[52] and two used the last digit of the patient's medical number to randomise.[50,51] The remaining 32 trials included 29 studies comparing an AI-CVC with a standard CVC; two comparing an AI-CVC with another AI-CVC and one trial that compared a standard CVC with two different AI-CVCs. Reports of studies which did not fulfil the inclusion criteria and the reasons for exclusion are listed in Appendix 6.

Table 6 lists included studies by type of catheter. Of the 32 included trials, 13 compared standard CVCs with AI-E-CVCs. The most frequently compared externally coated AI-E-CVC was CHSS. A further nine trials compared standard CVCs with AI-IE-CVCs; the most frequently compared AI-IE-CVC was CHSS. Five trials compared standard CVCs with those impregnated with an antibiotic. Minocycline rifampicin (MR) was used in four trials and miconazole and rifampicin in one trial.

Three trials compared AI-CVCs with AI-CVCs, although one of these[71] included three arms and also compared the treatment groups with a standard CVC. An additional two trials were not comparable to other groupings. One of these compared an AI-CVC with a heparin-treated standard CVC[12] and the other a standard tunnelled CVC with a silver impregnated cuff.[72]

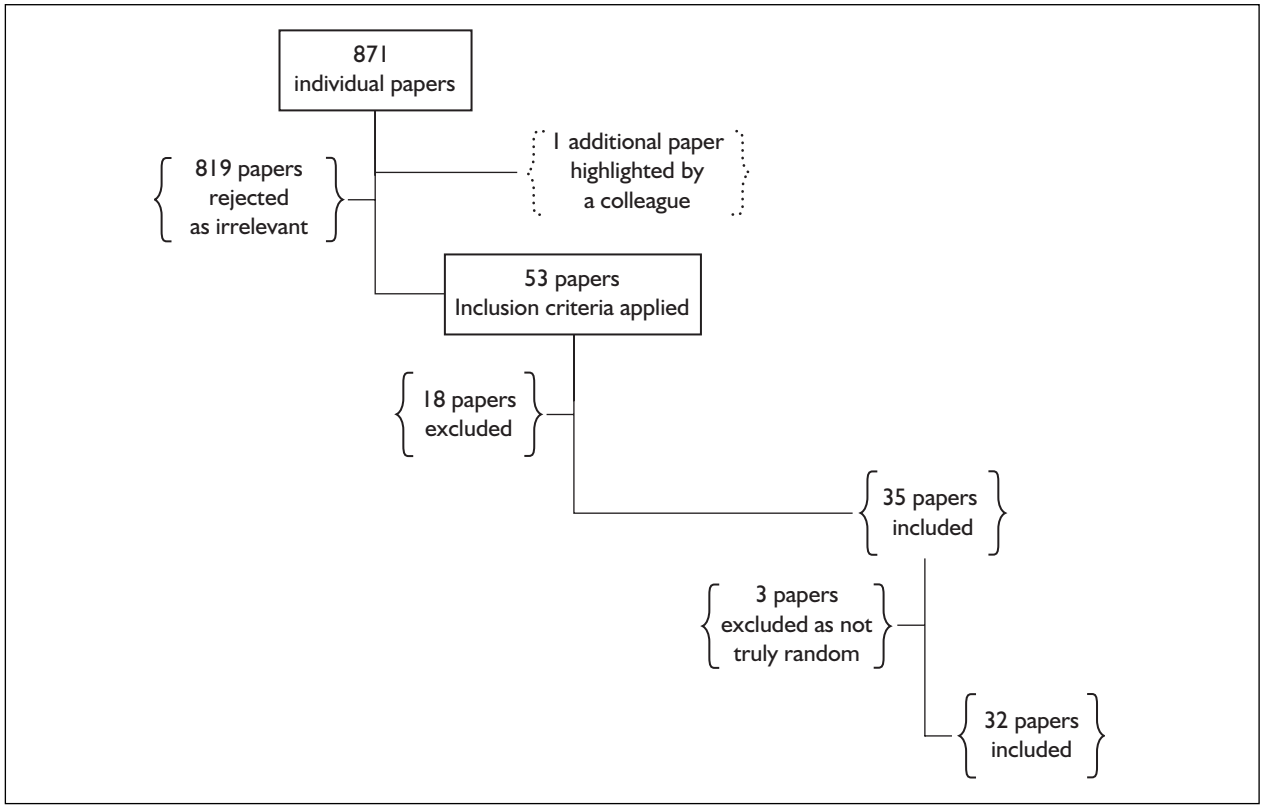

FIGURE 1 *Flow diagram showing the selection of trials*

TABLE 6 *Summary of included clinical studies*

Trial	Control		Treatment
Standard CVC vs AI-E-CVC			
Bach, 1996[53]	Standard		CHSS
Pemberton, 1996[54]	Standard		CHSS
Van Heerden, 1996[55]	Standard		CHSS
George, 1997[56]	Standard		CHSS
Logghe, 1997[57]	Standard		CHSS
Maki, 1997[58]	Standard		CHSS
Tennenberg,1997[59]	Standard		CHSS
Trerotola, 1998[60]	Standard		Silver
Bach, 1999[61]	Standard		Silver
Collin, 1999[62]	Standard		CHSS
Hannan, 1999[63]	Standard		CHSS
Sheng, 2000[64]	Standard		CHSS
Theaker, 2002[65]	Standard		CHSS
Standard CVC vs AI-IE-CVC			
Boswald, 1999[66]	Standard		Silver impregnated
Moss, 2000[67]	Standard		Benzalkonium chloride impregnated
Jaeger, 2001[68]	Standard		Benzalkonium chloride impregnated
Stoiser, 2002[69]	Standard		Silver impregnated
Bong, 2003[16]	Standard		Silver impregnated
Corral, 2003[14]	Standard		Silver impregnated
Brun-Buisson, 2004[13]	Standard		CHSS +
Jaeger, 2005[8]	Standard		CHSS +
Rupp, 2005[18]	Standard		CHSS +
Standard CVC vs AI-A-CVC			
Raad, 1997[38]	Standard		Minocycline rifampin
Chatzinikolaou, 2003[15]	Standard		Minocycline rifampin
Hanna, 2004[11]	Standard		Minocycline rifampin
Leon, 2004[10]	Standard		Minocycline rifampin
Yücel, 2004[9]	Standard		Miconazole and rifampicin
AI-CVC vs AI-CVC			
Darouiche, 1999[70]		Minocycline rifampin	CHSS
Marik, 1999[71]	Standard	CHSS	Minocycline rifampin
Ranucci, 2003[17]		Benzalkonium chloride treated	Silver, carbon and platinum
Other			
Babycos, 1993[72]		Tunnelled standard	Silver-impregnated cuff
Carrasco, 2004[12]		Heparin	CHSS

CHSS, chlorhexidine and silver sulfadiazine molecularly bonded to the outer wall of the CVC body only.
CHSS +, chlorhexidine and silver sulfadiazine molecularly bonded to the outer wall of the CVC body, the inner lumens, the inside and outside of the hub, and the internal and external walls of the extension lines applied to both the internal and external surface of the CVC.

Quality assessment

Results of the methodological quality assessment of studies are presented in *Table 7* using the criteria based on CRD Report No. 4 (see Appendix 4).[44] The overall methodological quality of included studies was poor, with almost half of the studies failing to report relevant methodology; most noticeably, the method of randomisation, blinding procedures and allocation concealment.

Twenty studies reported the method of randomisation, with 19 being truly random and one unclear. Allocation concealment was reported by 17 studies, of which ten were fully concealed.

For the 15 trials permitting more than one CVC per patient, randomisation was conducted by either randomising the CVCs to be inserted ($n = 6$)[11,38,57,58,64,70] or randomising patients who were due to have a CVC inserted ($n = 9$).[12–14,16,54,56,62,63,65]

TABLE 7 *Quality assessment of included studies*

Checklist items:	Randomisation			Baseline comparability		Eligibility criteria specified	Co-interventions identified	Blinding				Withdrawals		ITT
Study	Truly random	Allocation concealment	Number stated	Presented	Achieved			Assessors	Administration	Participants	Procedure assessed	>80% in final analysis	Reasons stated	
Babycos, 1993[72]	NS	NS	✓	✓×	✓	✓[b]	NS	NS	NS	NS	NS	✓	NA	NS
Bach, 1996[53]	NS	NS	NS	NS	NS	✓	✓	NS	NS	NS	NS	NS	NS	×
Pemberton, 1996[54]	✓	×	✓[r]	✓	✓	✓	✓	✓	×	NS[s]	NS	✓	✓	×
Van Heerden, 1996[55]	✓[a]	×[a]	✓	✓	✓	✓	✓[i]	×[a]	×[a]	×[a]	NS	✓	✓[z]	×
George, 1997[56]	✓	NS	✓×[d]	✓×	✓×	✓	✓	✓	×	NS	NS	✓	✓	NS
Logghe, 1997[57]	✓[a]	✓[a]	✓[j]	✓	✓	✓	✓	×[a]	✓[m]	✓[m]	NS	✓	×	✓[n]
Maki, 1997[58]	✓×[n]	✓	✓×[j]	✓	✓×	✓	✓	✓	✓	✓	NS	✓	✓	×
Raad, 1997[38]	✓	✓	✓[j]	✓	✓	✓	✓	NS	✓	✓	NS	×	✓	✓[t]
Tennenberg, 1997[59]	✓	×	✓	✓	✓	✓	✓[i]	×	×	×	NA	✓	✓	×
Trerotola, 1998[60]	✓[a]	✓×[y]	✓	✓	✓	✓	✓[i]	×	×	×	NA	✓	✓	×
Bach, 1999[61]	NS	NS	✓	✓	✓	NS	✓[c]	✓	NS	NS	NS	✓	✓	×
Boswald, 1999[66]	✓	NS	✓[d]	✓	✓×	✓	✓	NS	NS	NS	NS	×	✓	×
Collin, 1999[62]	✓	NS	✓[d]	✓	✓×	✓	✓	NS	NS	NS	NS	✓	✓	×
Darouiche, 1999[70]	✓	✓	✓[j]	✓	✓	✓×	✓	✓	✓	✓	NS	✓	✓	×
Hannan, 1999[63]	NS	NS	✓[j]	NS	✓[k]	✓	✓	NS	NS	NS	NS	✓	NA	NS
Marik, 1999[71]	✓	NS	×[dd]	✓	✓	✓×[o]	✓[i]	NS	NS	NS	NS	✓	✓	×
Moss, 2000[67]	✓[q]	✓×	✓[r]	✓	✓	✓	✓	NS	NS	NS	NS	✓	✓	×
Sheng, 2000[64]	NS	NS[u]	✓[d]	✓	✓	✓	✓[i]	✓	✓	NS[v]	NS	✓	NA	×
Jaeger, 2001[68]	NS	NS	✓[j]	✓	✓	✓	✓	✓	×	NS	NS	✓	NA	✓
Stoiser, 2002[69]	NS	NS	✓[j]	✓	✓	NS[w]	✓	NS	NS	NS	NS	×	✓	×
Theaker, 2002[65]	NS	NS	✓[d]	NS	✓	✓[x]	✓[i]	NS	NS	NS	NS	NS	NS	×
Bong, 2003[16]	✓	✓	✓[d]	✓[e]	✓[e]	✓	✓	NS	NS	NS	NS	✓	✓	✓[f]
Chatzinikolaou, 2003[15]	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	NS	✓	✓	NS[h]
Corral, 2003[14]	NS	NS	✓[j]	✓	✓×	✓	✓	NS	NS	NS	NS	✓	✓	×
Ranucci, 2003[17]	✓	NS	✓[r]	✓	✓	✓	✓[i]	NS	NS	NS	NS	✓	✓	×
Brun-Buisson, 2004[13]	NS	✓	✓	✓	✓[g]	✓	✓	✓	✓	✓	NS	✓	✓	×
Carrasco, 2004[12]	NS	×	✓	✓	✓	✓	✓	✓	×	×	NS	✓	✓	×
Hanna, 2004[11]	✓	✓	✓[j]	✓	✓	✓	✓	✓	×[a]	✓	NS	✓	✓	×
Leon, 2004[10]	✓	✓	✓	✓	✓×	✓	✓	✓	✓	✓	NS	×	✓	×[l]
Yücel, 2004[9]	✓[cc]	✓	✓[aa]	✓	✓	✓	✓	×	×	×	NA	×	✓	×
Jaeger, 2005[8]	NS	NS	✓[j]	✓	✓	✓	✓	✓	×	NS	NS	✓	×	✓
Rupp, 2005[18]	✓	✓×[bb]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓×

✓, Yes (item adequately addressed); ×, no (item not adequately addressed); ✓/×, partially (item partially addressed); ITT, intention-to-treat; NA, not applicable; NS, not stated.

continued

TABLE 7 *Quality assessment of included studies (cont'd)*

[a] Information clarified through correspondence with authors (see Appendix 7).
[b] Inclusion criteria unclear.
[c] Use of antibiotics was noted under methods of trial, but does not explicitly report what they were.
[d] The numbers of CVCs inserted were stated, but it is unclear if these were at randomisation.
[e] Baseline data presented by CVCs.
[f] Intention-to-treat (ITT) analyses were conducted but not presented.
[g] The number of complications on insertion was different between the two groups. Otherwise they were comparable.
[h] Although use of ITT analysis not explicitly stated, all patients were followed until the CVC was removed.
[i] Use of antibiotics not reported.
[j] CVCs were randomised at insertion and the number inserted is stated.
[k] As stated.
[l] ITT presented as the primary analysis.
[m] Stated as double blind.
[n] Although not explicitly stated, it appears to include ITT analysis (i.e. patients are analysed in the group to which they have been randomised).
[o] 'Preset randomisation schedule' used, but not specified explicitly.
[p] Stated in the abstract that trial population included intensive care patients requiring new CVCs, exclusion criteria not reported.
[q] Randomisation system consisted of sequentially sealed envelopes.
[r] The number of patients enrolled is stated. It is unclear if this was the number randomised.
[s] This is unclear; however, it is stated that a double-blind approach was not possible.
[t] It is stated that the analyses included all patients enrolled in the trial.
[u] Not explicitly stated how the allocation was concealed.
[v] Although not explicitly reported, it is highly likely that the participants were also blinded.
[w] Inclusion and exclusion criteria not reported; it is, however, stated in the abstract that the trial population includes a cohort of immunocompromised patients.
[x] Exclusion criteria not reported.
[y] Mentions use of sealed envelopes, but randomisation technique not reported.
[z] Although the reasons for withdrawals were stated, patient numbers for each reason were not provided.
[aa] Only total number of patients randomised is reported; number of patients in each intervention arm is unknown.
[bb] States that allocation was concealed, but does not state how it was concealed.
[cc] Computer-generated randomisation was concealed by use of opaque envelopes.
[dd] Total number stated only.

Of these trials, 14 analysed the data by CVC and one analysed by person (although no further details on methods used were available). Although Maki[58] analysed the data by catheter, CRBSI was also analysed by person.

The numbers of patients or CVCs randomised were reported for 30 trials. Although 19 of these studies did not explicitly state the number randomised, ten of the 19 stated the number of CVCs inserted and elsewhere had indicated that randomisation was at insertion; however, six trials stated the number of CVCs inserted but gave no indication whether this corresponded to numbers randomised. A further three trials stated the number of patients enrolled, but again did not state whether this corresponded to numbers randomised.

Two trials using more than one CVC per patient reported either the number of CVCs or patients randomised and therefore the number of patients reported was considered partially reported (one trial that had randomised by CVC only reported the number of CVCs randomised, and one trial that randomised patients only reported the number of CVCs).

Baseline comparability information was adequately presented in 27 trials and partially presented in two. The remaining three trials did not report any baseline comparability. Achievement of baseline comparability was reported by 31 trials, with 25 stating that they achieved comparability and six that they partially achieved comparability.

Eligibility criteria were specified in 30 trials, although two of these trials only partially specified the criteria. Co-interventions were identified in 31 trials.

The blinding procedures used in the trials were poorly reported. The blinding of assessors occurred in only 14 trials, with 13 trials failing to report whether assessors were blinded. Five trials stated that assessors were not blinded.

Treatment administrators were blinded in eight trials and were not blinded in 11 trials. The remaining 13 trials failed to report whether administrators were blinded.

It was stated that participants were blinded in nine trials and not blinded in five trials. Eighteen trials did not report whether participants were blinded. No trials assessed the effectiveness of the blinding procedure.

The majority of trials (25) included more than 80% of the original population in the final analysis. Two trials did not report the percentage of patients included in the final analysis and five trials lost more than 20% of the patients in the final analysis. The reasons for attrition were stated in 23 of the 32 trials. Finally, ITT analyses were carried out in only four trials.

Participant characteristics

Details of the characteristics of the patients included in the trials are shown in *Table 8*.

Number of patients and CVCs included in the RCTs

A variety of randomisation methods was used in the trials, with some trials stating the number of CVCs randomised rather than the number of patients randomised. Differences in randomisation methods cause problems when describing the number of patients and CVCs randomised and analysed. For studies including only one CVC per patient, the numbers are the same; however, for the 15 trials reporting more than one CVC per patient the numbers differ. The same problem occurs at analysis, with some trials reporting the number of CVCs analysed, but failing to report the number of patients analysed.

The total number of patients randomised was calculable in 29 studies; these studies reported a total of 7716 patients. Of the additional three studies, two reported the number of CVCs randomised (n = 86 and 442)[56,58] and one failed to report any numbers randomised.[73]

The total number of patients analysed was also calculable in 29 trials and they reported 6634 patients. The three trials not reporting the number of patients analysed included a total of 737 CVCs (n = 270, 235 and 232).[16,64,65] Therefore, the number of patients analysed was in the range of 6634–7371.

Two of the 15 studies permitting more than one CVC stated the number of CVCs randomised and not the number of patients randomised.[56,58]

Reasons for attrition

In these types of studies the attrition rate would be expected to be low. However, two studies failed to report the number of patients lost to follow-up and five studies had more than 20% attrition. Reasons for withdrawals were stated in all of these five studies and a further 19 studies. There were

TABLE 8 *Participant characteristics*

Study	Group	No. of patients	No. of CVCs	Reasons for attrition	No. of CVCs per patient	Age (years)	Males (%)	Duration (days)
Babycos, 1993[72]	Control	Randomised = 16 Analysed = 16	Randomised = 16 Analysed = 16	NS	1	NS	NS	Mean = 13.3 (range = 3–28)
	Treatment	Randomised = 17 Analysed = 17	Randomised = 17 Analysed = 17					Mean = 11.76 (range = 3–36)
Bach, 1996[53]	Control	Inserted and analysed = 117	Analysed = 117 Double lumen = 59 Triple lumen = 58	NS	1	NS	NS	
	Treatment	Inserted and analysed = 116	Analysed = 116 Double lumen = 57 Triple lumen = 59					
Pemberton, 1996[54]	Control	Analysed = 40	Randomised = 88[a] Analysed = 72[a] Analysed = 40	Non-evaluable = 16 Died = 4 Misplaced = 4 Emergent CVC changes = 3 Hospital transfer = 1 Missing chart = 1 No reason = 3	>1 Unclear if they were of the same type	Mean = 48 (SD 15)	58	Mean = 11 (SD 6)
	Treatment	Analysed = 32	Analysed = 32			Mean = 50 (SD 19)	66	Mean = 10 (SD 6)
Van Heerden, 1996[55]	Control	Randomised = 29 Analysed = 26	Randomised = 29 Analysed = 26	<5 days or if died during the 5-day period = 3	1	Mean = 52 (range 16–82)	65	Study period 5–7 days
	Treatment	Randomised = 32 Analysed = 28	Randomised = 32 Analysed = 28	<5 days or if died during the 5-day period = 4		Mean = 45 (range 13–88)	68	
George, 1997[56]	Control	60	Randomised = 86[a] Analysed = 35	Deviation from protocol, contamination of tip or death = 7	>1 Could be different types	(Range 19–60)	NS	
	Treatment		Analysed = 44					
Logghe, 1997[57]	Control	538	342	0	>1 Unclear if they were of the same type[b]	Mean = 50 (SD 15)	57	Sum = 6895 days Mean = 20 (SD 12)
	Treatment		338	0		Mean = 51 (SD 15.5)	54	Sum = 6931days Mean = 20 (SD 13)

continued

TABLE 8 *Participant characteristics (cont'd)*

Study	Group	No. of patients	No. of CVCs	Reasons for attrition	No. of CVCs per patient	Age (years)	Males (%)	Duration (days)
Maki, 1997[58]	Control	Analysed = 86	Randomised = 215 Analysed = 195	Removed within 8 hours or could not be cultured = 20	>1 Could be different types	Mean = 47 (SD 18)	NS	Mean = 145 (SD 82 hours)
	Treatment	Analysed = 72	Randomised = 227 Analysed = 208	Removed within 8 hours or could not be cultured = 19		Mean = 49 (SD 18)		Mean = 143 (SD 67 hours)
Raad, 1997[38]	Control	Randomised = 281 Analysed = 251	Randomised = 151 Analysed = 136	Removed without subsequent culture = 32	>1 Unclear if they were of the same type	Median = 56 (range 17–88)	61	Median = 6 (range 1–21)
	Treatment		Randomised = 147 Analysed = 130			Median = 58 (range 19–87)	59	Median = 6 (range 1–28)
Tennenberg, 1997[59]	Control	Analysed = 145 Double lumen = 100 Triple lumen = 45	Randomised = 352[a] Analysed = 145 Double lumen = 100 Triple lumen = 45	<48 hours of catheterisation = 34 Incomplete cultures = 26 Ongoing sepsis from another source = 3 Other reasons (CVC not inserted, wrong CVC inserted, CVC misplaced and CVC accidentally removed) = 7	1	Mean = 57.9 (SD 1.1)	NS	Mean = 5.3 (SD 0.2)
	Treatment	Analysed = 137 Double lumen = 90 Triple lumen = 47	Analysed = 137 Double lumen = 90 Triple lumen = 47			Mean = 59.2 (SD 1.1)		Mean = 5.1 (SD 0.2)
Trerotola, 1998[60]	Control	Randomised = 50 Analysed = 44	Randomised = 50 Analysed = 44	Enrolled after removal of their initial catheter = 6	1	Mean = 50	61	Mean = 125
	Treatment	Randomised = 50 Analysed = 47	Randomised = 50 Analysed = 47	Enrolled after removal of their initial catheter = 3		Mean = 53	53	Mean = 61
Bach, 1999[61]	Control	Randomised = 36 Analysed = 33	Randomised = 36 Analysed = 33	Transferred to other hospitals = 3	1	NS	73	Mean = 4.06 (SD 2)
	Treatment	Randomised = 38 Analysed = 34	Randomised = 38 Analysed = 34	Transferred to other hospitals = 4				Mean = 4.49 (SD 2.3)
Boswald, 1999[66]	Control	*In situ* for >4 days = 150 Analysed = 79	Remained in place for ≥5 days = 150 Analysed = 79	In place <5 days = 21[a] Not assessable = 71	1	Median = 53	71	Median = 8 (range 5–51) (sig. different)
	Treatment	*In situ* for >4 days = 115 Analysed = 86	Remained in place for ≥5 days = 113 Analysed = 86	Not assessable = 27		Median = 55	56	Median = 9 (range 5–27) (sig. different)

continued

TABLE 8 *Participant characteristics (cont'd)*

Study	Group	No. of patients	No. of CVCs	Reasons for attrition	No. of CVCs per patient	Age (years)	Males (%)	Duration (days)
Collin, 1999[62]	Control	Placed = 123[a] Analysed = 61	CVCs placed = 242[a] Analysed = 139	Died = 4 Pulled out by patient = 1	>1 Of the same type	Mean = 47.2	62	Mean = 7.3 (SD 5.0) (sig. different)
	Treatment	Analysed = 50	Analysed = 98			Mean = 46.4	74	Mean = 9.0 (SD 6.1) (sig. different)
Darouiche, 1999[70]	Control	Enrolled = 817[a] Analysed = 698[a] Analysed = 370	Randomised = 451 Analysed = 382	Removed without notification of trial coordinators = 84 Grossly contaminated during removal = 19 Other reasons = 24	>1 Could be different types	Median = 56	63	Mean = 8.2 Median = 7 (range 1–36)
	Treatment	Analysed = 350	Randomised = 414 Analysed = 356			Median = 56	59	Mean = 8.4 Median = 6 (range 1–55)
Hannan, 1999[63]	Control	228	Analysed = 177	0	>1 Unclear if they were of the same type	Median = 63 (range 30–86)		Mean = 7.6 (range 1–32)
	Treatment		Analysed = 174					Mean = 7.5 (range 1–17)
Marik, 1999[71]	Control	Analysed = 39	Analysed = 39	Not assessable = 7 Removed <24 hours = 3 Discarded in error = 4	1	Mean = 66 (SD 11)	NS	Mean = 6 (SD 4)
	Treatment	Analysed = 36	Analysed = 36			Mean = 63 (SD 10)		Mean = 6 (SD 3)
	Treatment2	Analysed = 38	Analysed = 38			Mean = 64 (SD 12)		Mean = 6 (SD 3)
Moss, 2000[67]	Control	Randomised = 118 Analysed = 98	Randomised = 118 Analysed = 98	Non-evaluable = 20	1	Mean = 61	NS	Mean = 102 hours
	Treatment	Randomised = 117 Analysed = 106	Analysed = 106	Non-evaluable = 11		Mean = 59		Mean = 91 hours
Sheng, 2000[64]	Control	204	122	NS	>1 Could be different types	Mean = 61 (SD 18)	62	Mean = 8.2 (SD 4.6)
	Treatment		113			Mean = 64 (SD 18)	60	Mean = 9.1 (SD 5.5)

continued

TABLE 8 *Participant characteristics (cont'd)*

Study	Group	No. of patients	No. of CVCs	Reasons for attrition	No. of CVCs per patient	Age (years)	Males (%)	Duration (days)
Jaeger, 2001[68]	Control	25	Analysed = 25	0	1	Median = 44	NS	Mean = 19.3 (SD 11.5)
	Treatment	25	Analysed = 25	0		Median = 45		Mean = 14.8 (SD 7.2)
Stoiser, 2002[69]	Control	Randomised = 157[a] Analysed = 47	Randomised = 157[a] Analysed = 47	Excluded owing to removal of CVC before day 3, accidental removal of CVC, transfer of patient to another hospital or death = 57	1	Median = 52 (range 24–81)	55	Median = 11 (range 4–46)
	Treatment	Analysed = 50	Analysed = 50			Median = 51 (range 20–84)	46	Median = 10.5 (range 3–39)
Theaker, 2002[65]	Control	181	131	NS	>1 Unclear if they were of the same type	Median = 62.5	NS	Mean = 7.2 Median = 6
	Treatment		101					Mean = 7.4 Median = 7
Bong, 2003[16]	Control	Inserted = 268	Randomised = 161 Analysed = 142	Removed without notification or lost to follow-up = 19	>1 Unclear if they were of the same type	Median = 59	92	Median = 14
	Treatment		Randomised = 143 Analysed = 128	Removed without notification or lost to follow-up = 15		Median = 55	95	Median = 10.5
Chatzinikolaou, 2003[15]	Control	Randomised = 140[a] Analysed = 130[a] Analysed = 64	Analysed = 64	Patient died before insertion attempt = 1[a] Unsuccessful insertion attempts = 4 Unsuccessful insertion attempts = 5	1	Mean = 57 (SD 14)	58	Mean = 8 (SD 6) Median = 7 (range 1–32)
	Treatment	Analysed = 66	Analysed = 66			Mean = 56 (SD 17)	67	Mean = 8 (SD 6) Median = 6 (range 1–32)

continued

TABLE 8 *Participant characteristics (cont'd)*

Study	Group	No. of patients	No. of CVCs	Reasons for attrition	No. of CVCs per patient	Age (years)	Males (%)	Duration (days)
Corral, 2003[14]	Control	Randomised = 80 Analysed = 65	Randomised = 131 Analysed = 103 Mean no. of protocol catheters per patient = 3 (SD 3, range 1–10) (significantly different)	Not cultured = 23 <4 days = 28	>1 Of the same type	Mean = 58 (SD 18) (range 16–81)	60	Mean = 14 (SD 7) (range 4–40)
	Treatment	Randomised = 95 Analysed = 80	Randomised = 126 Analysed = 103 Mean no. of protocol catheters per patient = 1.7 (SD 1, range 1–4) (significantly different)			Mean = 56 (SD 18) (range 17–80)	66	Mean = 12 (SD 7) (range 4–38)
Ranucci, 2003[17]	Control	Randomised = 306 Analysed = 277	Randomised = 306 Analysed = 277	Catheter contamination on removal = 10 Non-cultured catheters = 19	1	Mean = 65 (SD 15.3)	63	Mean = 9 (SD 6.9) Median = 7 (range 1–49)
	Treatment	Randomised = 301 Analysed = 268	Randomised = 301 Analysed = 268	Catheter contamination on removal = 12 Non-cultured catheters = 20 Intraoperative death = 1		Mean = 63.5 (SD 15.2)	68	Mean = 9.1 (SD 6.9) Median = 7 (range 3–43)
Brun-Buisson, 2004[13]	Control	Randomised = 175 1 CVC = 162: >1 CVC = 13	NS	0	>1 Of the same type	Mean = 58 (SD 18)	NS	Mean = 12 (SD 11.7) Median = 9
	Treatment	Randomised = 192 Analysed = 188 1 CVC = 180: >1 CVC = 11		Catheters not cultured = 3 Withdrew consent = 1		Mean = 59.2 (SD 17.8)		Mean = 10.5 (SD 8.8) Median = 8
Carrasco, 2004[12]	Control	Randomised = 98 Analysed = 91	Randomised = 139 Analysed = 132	Not cultivated = 7 CVCs from 7 patients	>1 Of the same type	Mean = 55 (SD 18.6)	46	Mean = 13.6
	Treatment	Randomised = 98 Analysed = 89	Randomised = 137 Analysed = 128	Not cultivated = 9 CVCs from 9 patients		Mean = 57 (SD 16.9)	42	Mean = 12.7

continued

TABLE 8 *Participant characteristics (cont'd)*

Study	Group	No. of patients	No. of CVCs	Reasons for attrition	No. of CVCs per patient	Age (years)	Males (%)	Duration (days)
Hanna, 2004[11]	Control	Randomised = 178 Analysed = 173	Analysed = 174	Failure of insertion = 5	>1 Of the same type	Mean = 52 (SD 14)	62	Mean = 63.01 (SD 30.80)
	Treatment	Randomised = 192 Analysed = 182	Analysed = 182	Failure of insertion = 10		Mean = 54 (SD 15)	57	Mean = 66.21 (SD 30.88)
Leon, 2004[10]	Control	Randomised = 237 Analysed = 180	Randomised = 237 Analysed = 180	Removed without notification = 37 Died = 17 Administrative reasons = 3	1	Mean = 59 (SD 18)	62	Mean = 9 (SD 5)
	Treatment	Randomised = 228 Analysed = 187	Randomised = 228 Analysed = 187	Removed without notification = 26 Died = 14 Administrative reasons = 1		Mean = 61 (SD 16)	65	Mean = 9 (SD 5)
Yücel, 2004[9]	Control	Randomised = 160 Analysed = 105	Analysed = 105	Not inserted = 26 Not evaluable = 29	1	Mean = 61 (range 21–80)	69	Mean = 6.7 Median = 6 (range 2–19)
	Treatment	Randomised = 156 Analysed = 118	Analysed = 118	Not inserted = 30 Not evaluable = 8		Mean = 62 (range 29–80)	69	Mean = 7.5 Median = 6 (range 2–36)
Jaeger, 2005[8]	Control	55	Analysed = 55	0	1	Median = 45	NS	Mean = 16.6 (SD 9.7) (range 1–58)
	Treatment	51	Analysed = 51	0		Median = 49		Mean = 14.3 (SD 8.2) (range 2–52)

continued

TABLE 8 *Participant characteristics (cont'd)*

Study	Group	No. of patients	No. of CVCs	Reasons for attrition	No. of CVCs per patient	Age (years)	Males (%)	Duration (days)
Rupp, 2005[18]	Control	Randomised = 780[a] Received = 393 Analysed = 362	Analysed = 362	Did not receive a catheter = 3[a] Not cultured = 31	1	Mean = 61 (SD 15.5)	60	*De novo* insertion: Mean = 142 hours (range 2–790 hours) Guidewire exchange: Mean = 120 hours (range 0.1–719 hours)
	Treatment	Received = 384 Analysed = 345	Analysed = 345	Not cultured = 39		Mean = 60 (SD 16.4)	61	*De novo* insertion: Mean = 123 hours (range 0.1–764 hours) Guidewire exchange: Mean = 124 hours (range 0.1–1109 hours)

[a] Total for all groups.
[b] Information received through contact with authors.

no losses in four studies, leaving the remaining four studies failing to give reasons for their attrition rates.

The reasons for attrition were varied and not always reported in sufficient detail, although the transfer of patients, CVC removal without notification and death were most frequently reported.

Where reported, rates of attrition were similar across arms for all but one trial.[66]

Gender and age of participants

The gender of patients was reported in 20 studies. The percentage of males ranged between 42.2% and 94.5%, with an average of 62.7%.

Patient's age was reported in 28 studies (nine reporting the median and 19 the mean age). The reported median ranged from 51 to 63 years, with the mean ranging from 45 to 66. The range of ages was reported by six studies; the youngest patient reported was 13 years old and the oldest 88 years old. The standard deviation (SD) was reported by 13 trials.

Duration

The duration of insertion was reported by all but two of the studies; however, one of these studies had a set trial period of between 5 and 7 days. The mean duration ranged from 3.8 to 66.21 days (n = 25) and the median from 6 to 14 days (n = 13). Two studies reported that there was a significant difference between the duration of the control CVC and the experimental CVC, with the duration of insertion longer in the treatment arm for both studies.[62,66]

Adverse events

Adverse events were reported by 16 trials (equating to 1838 standard CVCs and 2753 AI-CVCs) and four adverse events were reported: one dermatological allergic reaction in one standard case and two dermatological allergic reactions and two cases of hyperpigmentation in the AI-CVCs. All of the AI-CVCs with reported adverse events contained silver (silver coated and CHSS), which is known, in high concentrations, to have an effect on skin pigmentation.

Trial characteristics

Trial characteristics are presented in *Table 9*. Studies ranged in size from 33 to 707 patients. Nine studies had fewer than 100 patients in total; four studies had over 500 patients. The 18 studies that stated when the trials were conducted took place between 1990 and 2002. The publication dates ranged from 1993 to 2005. The trials were conducted in various countries, 12 in the USA, one in Australia, one in Taiwan and 18 in Europe, of which five were conducted in the UK. Eight studies were multicentred. Of the 16 studies conducted in intensive care units (ICUs) 12 were exclusively in this setting. Commercial research support for the trial was acknowledged in 20 of the trials and not stated in 11. The remaining trial was funded by the Bavarian government.

Design of included RCTs

Of the 32 included trials, 15 permitted one or more CVC per patient. For five of these, subsequent trial CVCs had to be of the same type as the initial trial CVC and three were rerandomised and could therefore differ. The remaining seven trials did not state whether subsequent CVCs had to be the same type as the initial CVC. Only one of these 15 trials analysed data exclusively by patient,[13] while one other trial included analyses by both patient and by CVC.[58] All reported results were extracted and where possible the results analysed by person were used in the analysis.

Number of lumens

Lumens are hollow, soft tubes that may be separated into two or more individual channels within a catheter. The majority of trials (19) only used triple-lumen CVCs, but four trials used double lumens only. Single-lumen and four-lumen CVCs were each used in one trial. The remaining seven trials used CVCs with differing numbers of lumens within the trial.

Number of CVCs exchanged over a guidewire

It was explicitly stated in 12 trials that exchanges over guidewires were not permitted. A further five trials reported that no catheters were exchanged over a guidewire and eight trials did not report whether guidewire exchange was permitted. Two trials used guidewires in all exchanges[61,72] and one trial in approximately 50% of exchanges (control group = 41%, treatment group = 53%).[58] The remaining four trials used guidewires in less than 50% of exchanges (average across groups of 30%,[18] 34%,[62] 6.6%[13] and 15.5%[14]).

Site of insertion

Of the 31 trials that reported the site of insertion, five inserted CVCs into the same vein in all patients. One of these inserted only into the femoral vein, two into only the subclavian vein

TABLE 9 *Trial characteristics*

Study	When trial conducted	Country	Setting in which trial was performed	Commercial research support	Group	No. catheter exchanges using a guidewire	Site
Babycos, 1993[72]	1990	USA	Hospital	NS	Both	100%	Subclavian
Bach, 1996[53]		Germany	NS	Arrow International	Both		Jugular only
Pemberton, 1996[54]	1993–1994	USA	Hospital	NS	Control	0	Internal jugular = 12/40 Subclavian = 28/40
					Treatment		Internal jugular = 8/32 Subclavian = 24/32
Van Heerden, 1996[55]	1995–1996[a]	West Australia	ICU	FAS Medical, UK	Both	NS	Subclavian and internal jugular[a]
George, 1997[56]	NS	UK	Hospital	Treatment catheters donated by Arrowgard	Control	0%	Femoral = 10/35 Internal jugular = 19/35 Subclavian = 6/35
					Treatment		Femoral = 9/44 Internal jugular = 27/44 Subclavian = 7/44
Logghe, 1997[57]	1993–1996	Belgium	Haematological oncology unit	NS	Control	Not allowed	Jugular = 24/342 Subclavian = 318/342
					Treatment		Jugular = 26/338 Subclavian = 312/338
Maki, 1997[58]	NS	USA	Medical/surgery ICU	In part by a grant from Arrow International	Control	41%	Femoral = 20% Internal jugular = 19% Subclavian = 61%
					Treatment	53%	Femoral = 22% Internal jugular = 18% Subclavian = 60%
Raad, 1997[38]	1994–1995	USA (5 centres)	ICU = 91 Other = 56	Cook Critical Care: the university cancer foundation	Control	Not allowed	Femoral = 18/151 Jugular = 46/151 Subclavian = 87/151
			ICU = 98		Treatment		Femoral = 11/147 Other = 53 Jugular = 46/147 Subclavian = 90/147

continued

TABLE 9 *Trial characteristics (cont'd)*

Study	When trial conducted	Country	Setting in which trial was performed	Commercial research support	Group	No. catheter exchanges using a guidewire	Site
Tennenberg, 1997[59]	1993–1995	USA	Hospital	Arrow International	Control	Not allowed	Femoral, jugular or subclavian
					Treatment		
Trerotola, 1998[60]	NS	USA	Hospital	Medcomp and Endoscopic Associates	Control	0[a]	Internal jugular = 44/44
					Treatment		Internal jugular = 47/47
Bach, 1999[61]	1995–1996	Germany	ICU	Trial catheters donated by Braun	Control	100%	Internal jugular vein = 71/74
					Treatment		Subclavian = 3/74
Boswald, 1999[66]	1995–1997	Germany	Hospital	Bavarian Government	Control	NS	Jugular = 71/79 Subclavian = 8/79
					Treatment		Jugular = 81/86 Subclavian = 5/86
Collin, 1999[62]	1995	USA	Emergency room = 18 Neurotrauma ICU = 8 Medical/surgery ICU	NS	Control	49/139	Femoral = 0% Jugular = 8% Subclavian = 92%
					Treatment	32/98	Femoral = 1% Jugular = 6% Subclavian = 93%
Darouiche, 1999[70]	1990–1997	USA (12 centres)	Hospital	Cook Critical Care	Control	Not allowed	Femoral = 11% Jugular = 36% Subclavian = 53%
					Treatment		Femoral = 8% Jugular = 38% Subclavian = 54%
Hannan, 1999[63]	NS	UK	ICU	NS	Control	Not allowed	Femoral = 11/177 Internal jugular = 139/177 Subclavian = 27/177
					Treatment		Femoral = 20/174 Internal jugular = 120/174 Subclavian = 34/174

continued

TABLE 9 *Trial characteristics (cont'd)*

Study	When trial conducted	Country	Setting in which trial was performed	Commercial research support	Group	No. catheter exchanges using a guidewire	Site
Marik, 1999[71]	NS	USA (4 centres)	ICU	CVCs donated by Arrow International and Cook Critical Care	Control	Not allowed	Femoral = 11/39 Internal jugular = 25/39 Subclavian = 3/39
					Treatment		Femoral = 6/36 Internal jugular = 26/36 Subclavian = 4/36
					Treatment 2		Femoral = 9/38 Internal jugular = 25/38 Subclavian = 4/38
Moss, 2000[67]	NS	UK	NS	Becton-Dickinson, Swindon, UK	Control	NS	Jugular = 93/98 Subclavian = 5/98
					Treatment		Jugular = 101/106 Subclavian = 5/106
Sheng, 2000[64]	1998–1999	Taiwan	ICU	NS	Control	Not allowed	Femoral = 11% Internal jugular = 87% Subclavian = 2%
					Treatment		Femoral = 5% Internal jugular = 92% Subclavian = 3%
Jaeger, 2001[68]	NS	Germany	Department of haematology and oncology	NS	Control	Not allowed	Internal jugular = 15/25 Subclavian = 10/25
					Treatment		Internal jugular = 14/25 Subclavian = 11/25
Stoiser, 2002[69]	1997	Germany (2 centres)	ICU	NS	Control	NS	Jugular = 15/47 Subclavian = 32/47
					Treatment		Jugular = 13/50 Subclavian = 37/50
Theaker, 2002[65]	NS	UK	ICU	Kimal provided the Arrow products	Control	NS	Femoral = 16/131 Jugular = 110/131 Subclavian = 5/131
					Treatment		Femoral = 20/101 Jugular = 76/101 Subclavian = 5/101

continued

TABLE 9 *Trial characteristics (cont'd)*

Study	When trial conducted	Country	Setting in which trial was performed	Commercial research support	Group	No. catheter exchanges using a guidewire	Site
Bong, 2003[16]	NS	UK	Hospital	Implemed, Boston, USA	Both	Not allowed	Subclavian
Chatzinikolaou, 2003[15]	2000–2002	USA	Cancer centre	Cook Critical Care	Both	NS	Femoral
Corral, 2003[14]	1999–2000	Spain	ICU	NS	Control	When protocol CVC introduced[b] = 18/103 (18%) When protocol CVC removed[b] = 17/103 (17%)	Femoral = 34/103[d] Jugular = 30/103 Subclavian = 39/103
					Treatment	When protocol CVC introduced[b] = 14/103 (14%) When protocol CVC removed[b] = 17/103 (17%)	Femoral = 42/103 Jugular = 15/103 Subclavian = 46/103
Ranucci, 2003[17]	2000–2001	Italy (10 centres)	Ward = 10/277 Emergency room = 13/277 Operating room = 133/277 ICU = 121/277	Edwards Life Sciences	Control	Not allowed	Femoral = 3/277 Jugular = 137/277 Subclavian = 137/277
			Ward = 7/268 Emergency room = 9/268 Operating room = 132/268 ICU = 120/268		Treatment		Femoral = 2/268 Jugular = 117/268 Subclavian = 149/268
Brun-Buisson, 2004[13]	NS	France (14 centres)	Medical ICU = 2 Surgical ICU = 9 Mixed units = 3	Arrow International	Control	*n* = 13/175 (7%)[c]	Jugular = 63/175 (36%) Subclavian = 112/175 (64%)
					Treatment	*n* = 11/191 (6%)[c]	Jugular = 59/191 (31%) Subclavian = 132/191 (69%)

continued

TABLE 9 *Trial characteristics (cont'd)*

Study	When trial conducted	Country	Setting in which trial was performed	Commercial research support	Group	No. catheter exchanges using a guidewire	Site
Carrasco, 2004[12]	9-month period	Spain	ICU	NS	Control	0	Femoral = 55/132 Internal jugular = 51//132 Subclavian = 26/132
					Treatment		Femoral = 61/128 Internal jugular = 41/128 Subclavian = 26/128
Hanna, 2004[11]	1999–2002	USA	Cancer centre	Cook Critical Care	Control	0[a]	PICC = 66/174 Subclavian single lumen = 24/174 Subclavian double lumen = 84/174
					Treatment		PICC = 64/182 Subclavian single lumen = 34/182 Subclavian double lumen = 84/182
Leon, 2004[10]	1999–2002	Spain (7 centres)	ICU	Grant from Cook Europe	Control	Not allowed	Internal jugular = 97/180 Subclavian = 83/180
					Treatment		Internal jugular = 99/187 Subclavian = 88/187
Yücel, 2004[9]	2000–2002	Germany	Hospital	Vygon	Control	NS	Internal jugular vein 97% (right side 95%)
					Treatment		Internal jugular vein 96% (right side 94%)
Jaeger, 2005[8]	2000	Germany	Department of haematology and oncology	NS	Control	Not allowed	Jugular = 48/55 Subclavian = 7/55
					Treatment		Jugular = 46/51 Subclavian = 5/51

continued

TABLE 9 *Trial characteristics (cont'd)*

Study	When trial conducted	Country	Setting in which trial was performed	Commercial research support	Group	No. catheter exchanges using a guidewire	Site
Rupp, 2005[18]	1998–2001	USA (9 centres)	ICU	Arrow International	Control	119/393 (30%)	Femoral = 23/393 Internal jugular = 234/393 Subclavian = 136/393
					Treatment	114/384 (30%)	Femoral = 22/384 Internal jugular = 220/384 Subclavian = 141/384

Single centre unless stated otherwise.
ICU, intensive care unit; PICC, peripherally inserted central catheter.
[a] Information clarified through correspondence with authors (see Appendix 7).
[b] If the insertion of the previous CVC occurred less than 72 hours before admission to the ICU, or if the patient needed a triple-lumen CVC at discharge from the ICU.
[c] Allowed only in cases of low to moderate suspicion of CVC infection, in the absence of severe sepsis or with obvious signs of infection at the CVC insertion site.
[d] More frequently in jugular; less frequently in femoral (significant).

and two into the jugular vein only. Of the remaining 25 trials, 13 inserted at least one CVC into a femoral vein. The percentage of insertions into the femoral veins for these 13 trials ranged from 0.7% to 48%. The jugular vein was used in 25 trials, with the percentage of insertions being in the jugular ranging from 6% to 96%, with 12 trials reporting more than 50% use of the jugular site. Finally, the subclavian vein was used in 25 trials. The percentage of insertions in the subclavian vein ranged from 2% to 93% and ten trials reported that more than 50% of insertions were inserted into the subclavian vein.

CVC practice characteristics

Practice characteristics are presented in *Table 10*. Each characteristic is important as each may affect the risk of a CRBSI.

Insertion operator

Twenty-two trials reported some detail on who inserted the CVC, with three of these stating that the operator was experienced, another four were anaesthetists, five were attending physicians and three were house staff. The remaining seven trials reported various people: one specialist, an ICU physician, upper level surgical residents, one of five interventional radiologists, ICU medical staff of specialist registrar grade or above, surgeons who inserted into the subclavian and a trained infusion therapy nurse who inserted PICCs, medical registrar and consultants. The experience of these individuals in the included trials cannot be assessed.

Insertion technique

All trials reported their insertion technique, with nine fully reporting what aseptic measures (e.g. cap, large sterile drapes) they used. A further 12 trials reported using maximal sterile barriers and two referenced papers by Maki[74,75] in the technique they used. A further trial reported using full aseptic technique. Five trials stated that they used an aseptic technique and three reported that insertions were conducted in sterile conditions.

Skin preparation

Twenty-eight trials reported the solution used in skin preparation. Eighteen trials used povidone iodine without alcohol and one chlorhexidine without alcohol. A further two trials used either povidone iodine or chlorhexidine without alcohol. The remaining seven trials used alcohol, three in conjunction with chlorhexidine, and four alcohol alone.

Dressing type

A total of 27 trials reported the type of dressing used, with 11 trials using sterile gauze and tape. The remaining 16 trials reported a variety of permeable, semi-permeable, occlusive, semi-occlusive and non-occlusive dressings. These dressings can be transparent and ten trials did report the use of transparent dressings.

Frequency of management

All but two trials reported the frequency of dressing changes and some reported the management of lines (changing of tubes and flushing). Most trials (11) changed dressings every 48 hours, but four changed them every 24 hours. Five trials reported changing them every 72 hours and one every 5 days. Three trials changed the dressings weekly and three, three times a week. The remaining three trials each changed them every 2–5 days, every 3–4 days and after every dialysis session.

Additional study characteristics

Additional study characteristics data (e.g. inclusion/exclusion criteria and primary outcomes) are provided in Appendix 8.

Approach to analyses

Once the data from the trials had been extracted, it was possible for the two reviewers (JH, KD) and the clinical expert (GS) to formulate a categorisation system that took into account the varied definitions of CRBSI and the differing microbiological diagnostic methods (see below). In addition, studies were grouped according to the pre-established confounding variables (randomisation, blinding, site and duration).

Planned categorisation

Primary outcome

The primary outcome for this review is CRBSI. As discussed in the section 'Diagnosis of CRBSI' (p. 3), there are several methods of identifying microorganisms. Traditionally, organisms isolated from the CVC and the bloodstream are regarded as identical if they are of the same species and morphological appearance, and have the same antibiotic sensitivity pattern. Recent research studies, however, using molecular fingerprinting have shown that apparently identical isolates may in fact be different on 20–40% of occasions.[38] *Table 11* categorises different studies as alpha or beta depending on whether molecular

TABLE 10 *Practice characteristics*

Study	Inserted by	Insertion technique	Skin preparation	Dressing type	Frequency of management
Babycos, 1993[72]	Upper level surgical residents or junior surgical residents under the direct supervision of an upper-level resident and/or surgical faculty member	Sterile gowns, gloves, caps and masks were worn by both the resident inserting the CVC and the first assistant. The patients were properly placed in the trendelenburg position with a roll between the shoulder blades and the head turned towards the opposite side. Vita cuff inserted using technique described by Maki[75]	10% PI	Semi-occlusive (Opsite)	Opsite dressing was changed on a routine basis every 5 days and as needed
Bach, 1996[53]	NS	Seldinger;[76] full barrier precautions	Alcoholic disinfectant	Dry gauze dressing	Every 72 hours
Pemberton, 1996[54]	Experienced resident at the bedside or in the operating room	Standard protocol for gowns, drapes, skin preparation and dressing	NS	Occlusive transparent	Inspected at least 5 times per week; dressings were changed for signs of infection or dressing non-occlusion, or at least every 7 days
Van Heerden, 1996[55]	Medical staff registrars and consultants[a]	Aseptic: included cleaning the proposed insertion site with chlorhexidine 0.5% in alcohol and then draping the insertion site with a sterile towel	Chlorhexidine 0.5% in alcohol	Transparent dressing (opsite IV 3000)	Day 3 hub cleaned
George, 1997[56]	Attending physician	Full aseptic	2% aqueous chlorhexidine-based skin preparation	Transparent bio-occlusive dressing	Dressing changed daily
Logghe, 1997[57]	Anaesthetist	Seldinger[76] under aseptic conditions	0.5% chlorhexidine in 70% isopropanol	Plain gauze[a]	Every 48 hours
Maki, 1997[58]	House officers	Masks, sterile gloves, surgical gowns and large sterile drapes; Seldinger[76] technique	10% PI applied with scrubbing for ⩾30 seconds	Sterile gauze and tape	Every 48 hours
Raad, 1997[38]	NS	MSB, use of sterile gown, sterile gloves, full sterile drapes, a mask and a cap	CG or a 10% PI scrub	Sterile gauze and taped securely	Every 72 hours
Tennenberg, 1997[59]	Resident surgical and medical house staff	Sterile Seldinger[76] and the CVC insertion kit	PI	Transparent	Dressing changes every other day and daily monitoring of the CVC site for signs of infection

continued

TABLE 10 *Practice characteristics (cont'd)*

Study	Inserted by	Insertion technique	Skin preparation	Dressing type	Frequency of management
Trerotola, 1998[60]	One of five interventional radiologists	Ultrasound-guided internal jugular vein puncture and fluoroscopically guided CVC placement under strict sterile technique	PI ointment	Non-occlusive dressing	Catheter was flushed after placement and each dialysis session; entrance site was inspected three times a week
Bach, 1999[61]	Staff anaesthesiologists and intensivists	Maximum barrier precautions (stated)	Alcoholic solution	Sterile gauze dressing	Every 48 hours
Boswald, 1999[66]	NS	Sterile conditions; Seldinger[76] technique	10% PI for 2 minutes	NS	Inspected every 48 hours
Collin, 1999[62]	Attending physician	Aseptically (Maki);[74] washed hands, sterile gloves, sterile gown, sterile sheets over entire bed	10% PI solution	Povidone iodine ointment and a transparent permeable polyurethane	Every 72 hours
Darouiche, 1999[70]	Attending physicians, house staff or supervised medical students	MSB precautions (stated)	10% PI	NS	Dressing changed three times a week
Hannan, 1999[63]	ICU medical staff of specialist registrar grade and above	Aseptically: large sterile drapes; Seldinger[76]	Betadine iodine solution	Sterile transparent semi-occlusive dressing	Every 48 hours
Marik, 1999[71]	House staff	Masks, gowns, gloves and drapes	10% PI	Transparent	Every 48 hours
Moss, 2000[67]	Anaesthetist	Strict aseptic technique (stated), Seldinger[76]	Sprayed with chlorhexidine 2.5% in industrial methylated spirit 70% which was allowed to dry for up to 2 minutes	Site cleaned and a non-occlusive transparent dressing applied	Every 72 hours
Sheng, 2000[64]	Senior residents or anaesthesiologists	Percutaneously using the Seldinger[76] technique wearing masks, sterile gloves and surgical gowns	10% PI, applied with scrubbing for ⩾30 Seconds	Sterile gauze and tape	Every 48 hours
Jaeger, 2001[68]	Attending physician	MSBs (stated); Seldinger[76]	10% PI	NS	Daily
Stoiser, 2002[69]	Experienced physician	Seldinger;[76] caps, masks, sterile gloves, coats and drapes	1 mg hexidine, 314 mg isopropranol and 28 mg *N*-propranol (corresponding to a 75% solution of alcohol in water)	Sterile gauze and tape	NS

continued

TABLE 10 *Practice characteristics (cont'd)*

Study	Inserted by	Insertion technique	Skin preparation	Dressing type	Frequency of management
Theaker, 2002[65]	NS	Aseptically (stated); Seldinger[76]	NS	Sterile semi-transparent semi-occlusive dressing	48 hours
Bong, 2003[16]	One person	Aseptically (large sterile drapes); Seldinger[76] technique	PI was applied to the skin insertion site and surrounding area and allowed to dry	Semi-permeable transparent dressing	Infusion lines were changed every 48 hours by the nurses and the dressings were changed once a week unless crumpled
Chatzinikolaou, 2003[15]	NS	MSB precautions followed (stated)	NS	NS	After every dialysis session
Corral, 2003[14]	Specialist intensive care physicians	Aseptically by the standard Seldinger[76] technique using sterile gloves, drapes, masks and gowns. Catheters were sutured in place and the insertion sites were swabbed with povidone iodine solution (0.1 g/mi)	PI	Sterile gauze dressings impregnated with PI	Every 72 hours
Ranucci, 2003[17]	Operator	Sterile; barrier precaution (sterile gloves, gown and mask for routine insertion)	Chlorhexide based = 26, PI based = 242 Chlorhexide based = 33, PI based = 244	Occlusive transparent medication	Every 48 hours
Brun-Buisson, 2004[13]	NS	Maximal barrier precautions during insertion and repositioning (stated)	NS	Gauze replaced within 48 hours by a transparent, semi-permeable dressing, to allow daily inspection of the insertion site	As clinically indicated, at 2–5-day intervals
Carrasco, 2004[12]	Attending physician	Full barrier precautions (stated)	Soap and disinfected with 10% PI	Non-transparent sterile gauze	Every 48 hours

continued

TABLE 10 *Practice characteristics (cont'd)*

Study	Inserted by	Insertion technique	Skin preparation	Dressing type	Frequency of management
Hanna, 2004[11]	Surgeons inserted subclavian CVCs and a trained infusion therapy nurse inserted the PICC[a]	MSB precautions using gowns, masks, sterile gloves and full sterile drapes	10% PI[a]	Occlusive = 110/174, non-occlusive = 41/174, both = 23/174 Occlusive = 128/182, non-occlusive = 40/182, both = 14/182	Patients come to hospital at least once a week for dressing change at infusion therapy department
Leon, 2004[10]	NS	MSBs (stated)	10% PI	Gauze	Three times a week
Yücel, 2004[9]	NS	MSB precautions, including mask, cap, sterile gown, gloves and drape	Scrubbed for 60 seconds with 72% alcohol (propanol), and excess solution had been wiped from the site with a sterile gauze	Sterile gauze	Every 24 hours
Jaeger, 2005[8]	Experienced physicians	MSBs (stated) Seldinger[76] technique	10% PI	NS	Dressing changed daily
Rupp, 2005[18]	Operators	Full sterile barrier precautions (stated)	10% PI	Transparent polyurethane	72–96 hours

CG, chlorhexidine gluconate; MSB, maximal sterile barrier; PI, povidone iodine.
[a] Information received from authors.

TABLE 11 *Key to terms*

Outcome	Category	Definition	Subcategory	Subcategory definition
CRBSI	α	Identical molecular fingerprint	S+	Clinical signs and symptoms of infection
			S–	No clinical signs or symptoms
	β	Phenotypically indistinguishable	S+	Clinical signs and symptoms of infection
			S–	No clinical signs or symptoms
	βX	Phenotypically indistinguishable, but blood was taken through the catheter, not via a peripheral vein	S+	Clinical signs and symptoms of infection
			S–	No clinical signs or symptoms
	θ	Recognised pathogen, but no link to line	S+	Clinical signs and symptoms of infection
			S–	No clinical signs or symptoms
Clinical symptoms	L	Local symptoms		NA
	S	Systemic symptoms		
Colonisation	A	Roll plate method of measuring colonisation		
	B	Brush method of measuring colonisation		
	C	Broth method of measuring colonisation		
	D	Other methods of measuring colonisation		
Local clinical signs only	I	Signs of infection, e.g. redness/pus		
	P	Pain at insertion site		

fingerprinting (α) or standard microbiological approaches (β) were used. Studies that did not provide evidence of a direct link between the bloodstream organism and the CVC colonisation were categorised as θ.

It is conventional to define CRBSI based on positive blood cultures taken from a peripheral vein. However, studies that reported CRBSI based only on blood cultures taken through the CVC itself were subcategorised as βX.

Some investigators include in their reports whether the microbiological diagnosis of CRBSI was associated with clinical symptoms or signs of systemic infection (e.g. fever, rigors). Such studies are subcategorised as S+; if associated clinical features were not reported the study was subcategorised as S–.

Surrogate outcomes

Where studies failed to define CRBSI according to strict microbiological criteria, clinical symptoms and signs were considered as end-points. These were classified as either L for local symptoms or S for systemic symptoms. Local symptoms could just indicate a local reaction or soreness as a result of surgery, whereas systemic symptoms (e.g. sweating, rigors) indicate an infection and are therefore more serious and have a higher associated risk of CRBSI.

Colonisation of catheter tips was frequently measured using different methods. Colonisation outcomes measured using the Maki roll plate method and taking a significant result to be equal to or greater than 15 CFU were categorised with an 'A', colonisation measured by the brush method was categorised as 'B' and colonisation measured by a broth solution was categorised as C. A category of 'D' was given to any other measure, such as one-off levels of colonisation taken as significant, meaning that category D was heterogeneous. Some studies used a combination of methods, and where the results for each category could not be extrapolated both category letters were used (e.g. A or B and A or C). The categories A–D were ordered categories, with A

representing the highest standard and D the lowest standard.

Finally, some studies reported outcomes of local signs, but not CRBSI or colonisation. These were further categorised with an 'I' for local signs of infection (e.g. redness) or a 'P' for pain.

Confounding variables

Randomisation
Trials were separated into two groups: truly randomised and randomisation method unclear.

Blinding
Trials were split into three groups: attempted, open and not stated. The attempted group included trials that had attempted blinding of the administrator or the assessor. The open group included trials that did not blind either the administrator or the assessor. The not stated group included trials where blinding was not commented on.

Catheter insertion site
These sites were jugular, subclavian and femoral. Where trials were heterogeneous for these insertion sites they were categorised as mixed.

Duration
Trials were split into four groups according to the duration of CVC insertion: less than 5 days, 5–12 days, 13–20 days and long term. Epidemiological studies have previously indicated that the longer a CVC remains in place, the greater the risk of eventual CRBSI. These time intervals were chosen because they best reflected the discontinuous study periods reported in the trials.

Implemented categorisation

Outcomes

CRBSI
This was reported in 26 of the studies. There were four different classifications of CRBSI: α, β, βX and θ (see above). Each of these could be further broken down into two additional categories (with signs of infection or not). However, trials categorised as θ were not included in the analysis as there is no reported link between the infection and the CVC and therefore this was considered an inadequate measure of CRBSI.

Clinical symptoms
There were two classifications for clinical symptoms, local and systemic. Only four studies reported local clinical symptoms and two of these were combined with other outcomes and therefore not comparable. One trial reported systemic clinical symptoms. Therefore, a meta-analysis could only be undertaken for the two studies reporting local clinical symptoms.

Colonisation
This was separated into five different classifications: A, C, A or B, A or C, and D (see above). Twenty-eight studies reported colonisation. However, group D (any other measure, e.g. one-off levels of colonisation taken as significant) was not included in the analysis as it was not comparable with the other groups. Therefore, three studies that only reported group D colonisation rates were excluded from the analysis, resulting in 25 studies being included in the analysis.

Local clinical signs only
There were two classifications for local clinical signs only: pain and signs of infection. One trial reported pain and five studies reported signs of infection; one trial did not report results for infection, but indicated that data for these outcomes were collected. One trial reported infection results by specific symptoms and as one patient could experience more than one symptom, results could not be grouped into the number of patients with local clinical signs only. Therefore, only four studies were included in the meta-analysis for infection.

The number of trials reporting each outcome is presented in *Table 12*.

For the following four subgroup analyses, only CRBSI and colonisation were investigated.

Randomisation
For trials reporting CRBSI, 13 trials stated method of randomisation and 11 were unclear. For trials reporting colonisation, 11 trials stated the method of randomisation and 12 were unclear.

Blinding
For CRBSI, 12 trials attempted some level of blinding, two were open and ten did not state whether blinding occurred. For colonisation, ten trials attempted some level of blinding, three trials were open and ten did not state whether blinding occurred.

Insertion site
For the purposes of the analysis studies reporting more than 90% of catheters inserted in a single site were categorised by that site. For CRBSI, one trial reported results for the femoral site, four reported for the subclavian site, three reported for the jugular site and 16 reported results for mixed

TABLE 12 *Number of studies measuring each outcome*

Outcome	Category	*n*
CRBSI	α S+	3
	α S–	1
	β S+	15
	β S–	6
	βX S+	2
	θ	2
Clinical symptoms	L	2
	S	1
	L + S	1
	Colonisation A + L	1
	Colonisation C + L	1
Colonisation	A	14
	A or B	1
	A or C	7
	C	6
	D	4
Local clinical signs only	I	5
	P	1

Some studies reported more than one outcome between and within 'outcome', therefore numbers do not equal 32 but 73 (see Appendix 7).

sites. For colonisation, one trial reported results for the femoral site, two reported for the subclavian site, four reported for the jugular site and 15 reported results for mixed sites. In these 15 mixed-site trials the proportion of CVCs inserted in each site was similar across the arms of the trials.

Duration

For CRBSI, no trials involved CVC insertion for less than 5 days, 16 trials lasted between 5 and 12 days, six trials were between 13 and 20 days, and one trial was long term. For colonisation, one trial involved CVC insertion for less than 5 days, 17 trials lasted between 5 and 12 days, four trials were between 13 and 20 days and one trial was long term. The majority of trials reported mean duration, although four trials were included that reported median duration.[16,38,66,69] It is likely that the data are skewed and means would overestimate the average length of time for which the catheters were inserted.

Trial grouping

Trials were grouped into those using CVCs treated with antibiotics (AI-A-CVC), those treated with an anti-infective extraluminally (AI-E-CVC) and those treated with an anti-infective both intraluminally and extraluminally (AI-IE-CVC) (see *Table 6*, p. 12).

Marik[71] reports a multiarm trial with two different treatment catheters being compared with a standard control catheter. For the overall analysis, the control group was split in half to compare with each treatment group. This is to ensure that each patient in the control group was included in the meta-analysis only once. In the subgroup analysis the full control group was used as we did not combine across subgroups.

Studies comparing head-to-head trials are reported separately as they are not comparable to the other studies.

Heparin is not an anti-infective agent and could have been grouped with the standard CVCs. However, studies that have looked at heparin-treated CVCs compared with standard CVCs have suggested that heparin may reduce CRBSI[77] and therefore they are not comparable with standard catheters and are discussed separately.

Chapter 4

Results

The following sections provide the results of the analyses. Each comparison was conducted separately for rates of CRBSI, clinical symptoms, colonisation and local clinical signs. However, as there were only two trials reporting clinical symptoms the results were uninformative and are not detailed here.

All studies

CRBSI

The pooled result suggests a statistically significant advantage for treated CVCs in comparison to standard catheters in reducing CRBSI (OR 0.45, 95% CI 0.34 to 0.60, 24 studies, $I^2 = 0\%$, fixed effects) (*Figure 2*). To inform the economic evaluation (see the section 'Economic evaluation for the NHS in England and Wales', p. 76), relative risk estimates were also calculated (RR 0.46, 95% CI 0.34 to 0.62).

Colonisation

The pooled result indicates a statistically significant reduction in risk of colonisation (RR 0.56, 95% CI 0.45 to 0.69, 23 studies, $I^2 = 62.4\%$, random effects). Heterogeneity was detected and a random-effects model was used to pool the results (*Figure 3*).

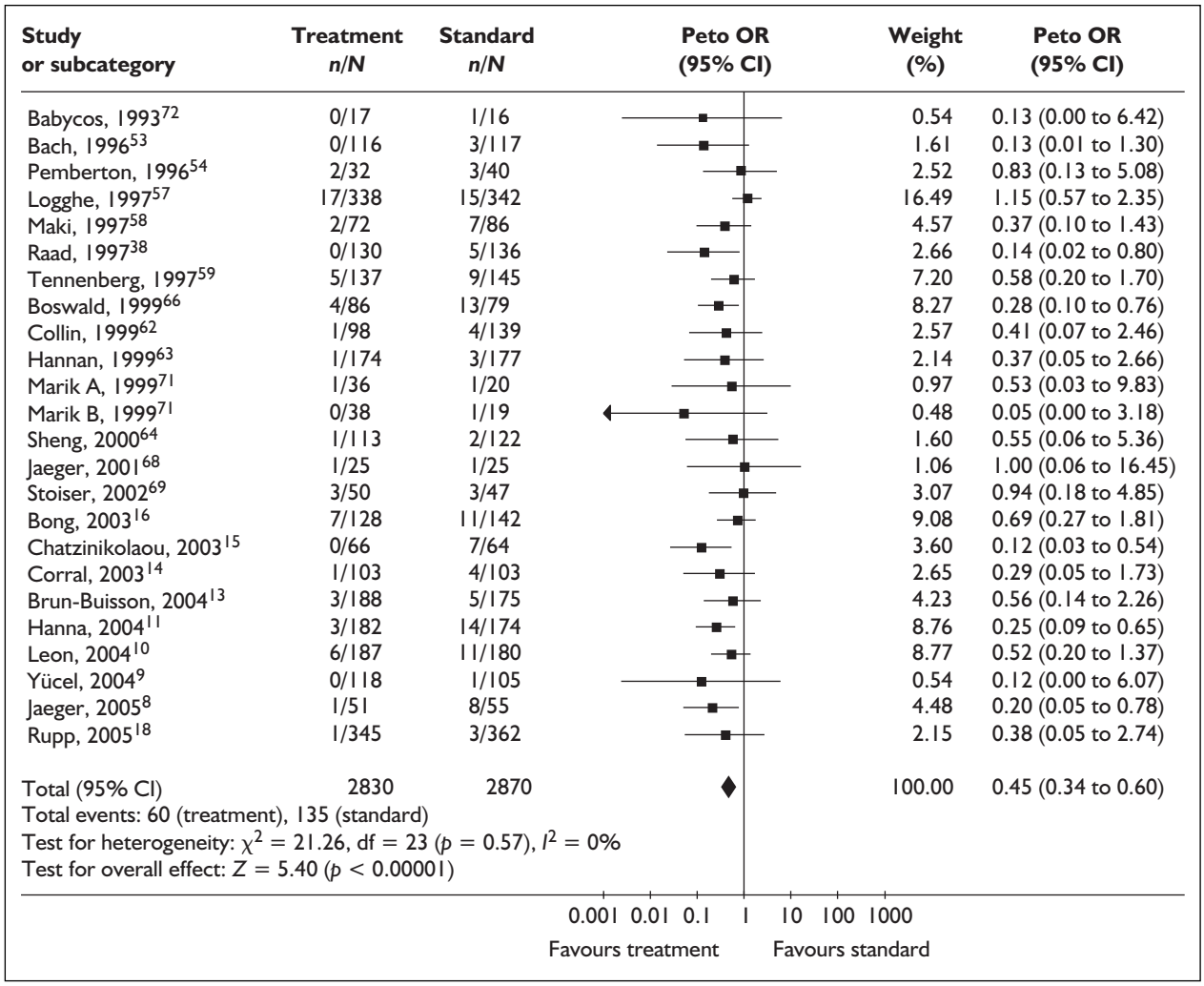

FIGURE 2 *CRBSI rates, all studies*

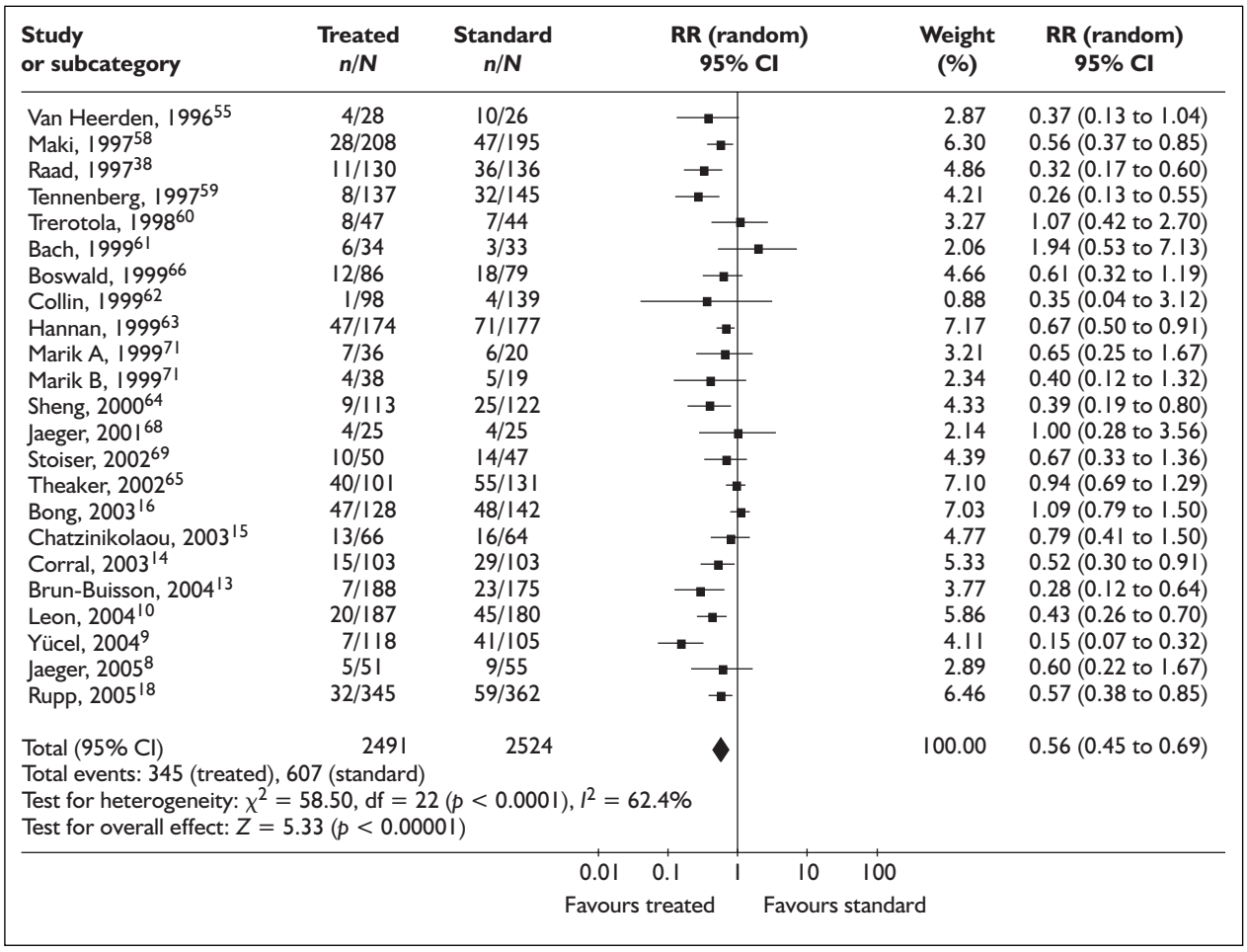

FIGURE 3 *Colonisation rates, all studies*

Local clinical signs only

A statistically significant difference was not detected (RR 0.90, 95% CI 0.65 to 1.25, six studies, $I^2 = 37.1\%$, fixed effects). Although there is large variability in the strength and direction of the effects, statistically significant heterogeneity was not detected. Therefore, the random effects result is also reported (in text only) (RR 0.90, 95% CI 0.53 to 1.54) (*Figure 4*).

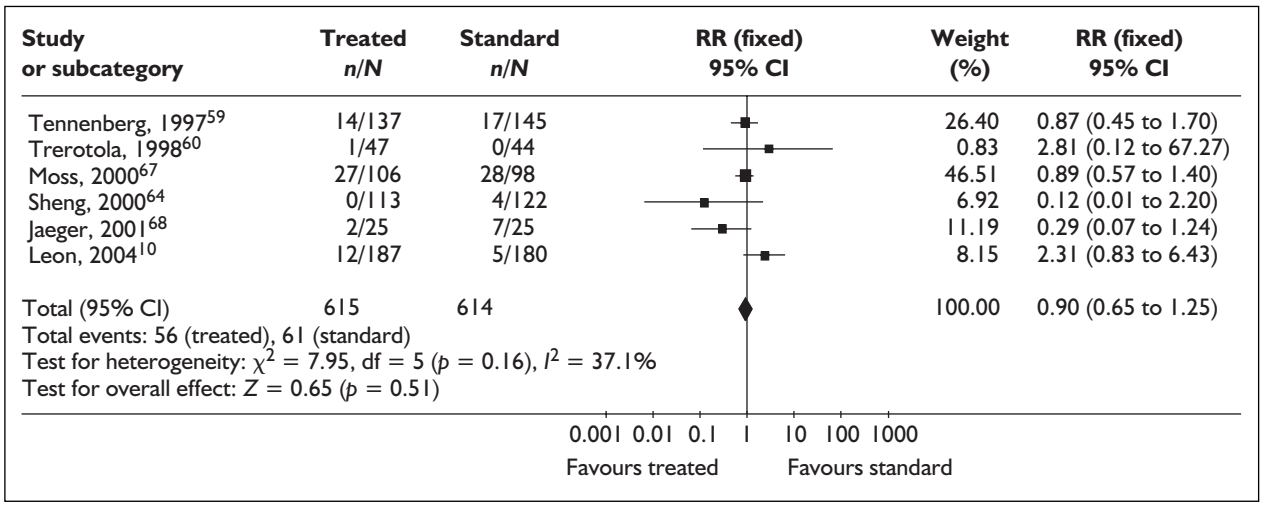

FIGURE 4 *Local clinical signs only rates, all studies*

Category of treated CVC

Subgroup analyses were carried out on AI-A-CVCs, AI-E-CVCs and AI-IE-CVCs compared with standard.

CRBSI

The OR favours treatment compared with standard for each of the three subgroups. However, the results for AI-A-CVCs (OR 0.26, 95% CI 0.15 to 0.46, six studies, $I^2 = 0\%$, fixed effects) and AI-IE-CVCs (OR 0.43, 95% CI 0.26 to 0.70, nine studies, $I^2 = 0\%$, fixed effects) are statistically significant and show a reduced risk of CRBSI. The AI-E-CVCs' only treatment effect of 0.67 (95% CI 0.43 to 1.06, nine studies, fixed effects) has a wider confidence interval and is non-significant (*Figure 5*).

Colonisation

The heterogeneity evident for colonisation, across all studies comparing a treated CVC with a standard catheter, is not explained by subgrouping the studies by type of treated catheter. The treatment effects indicate a statistically significant reduced risk of colonisation for those given treated catheters for all three groups (*Figure 6*).

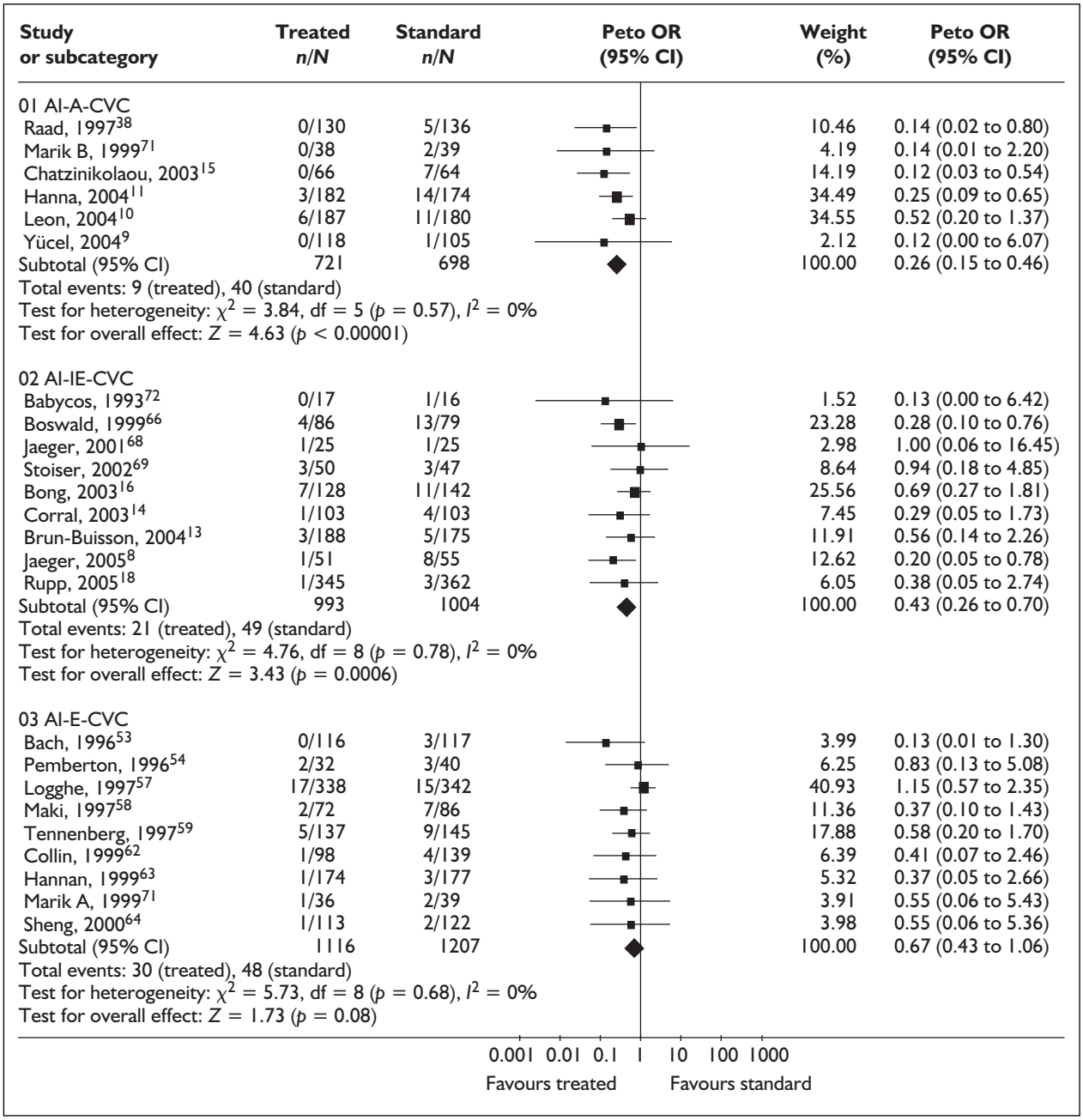

FIGURE 5 *CRBSI rates, subgrouped by category of treatment*

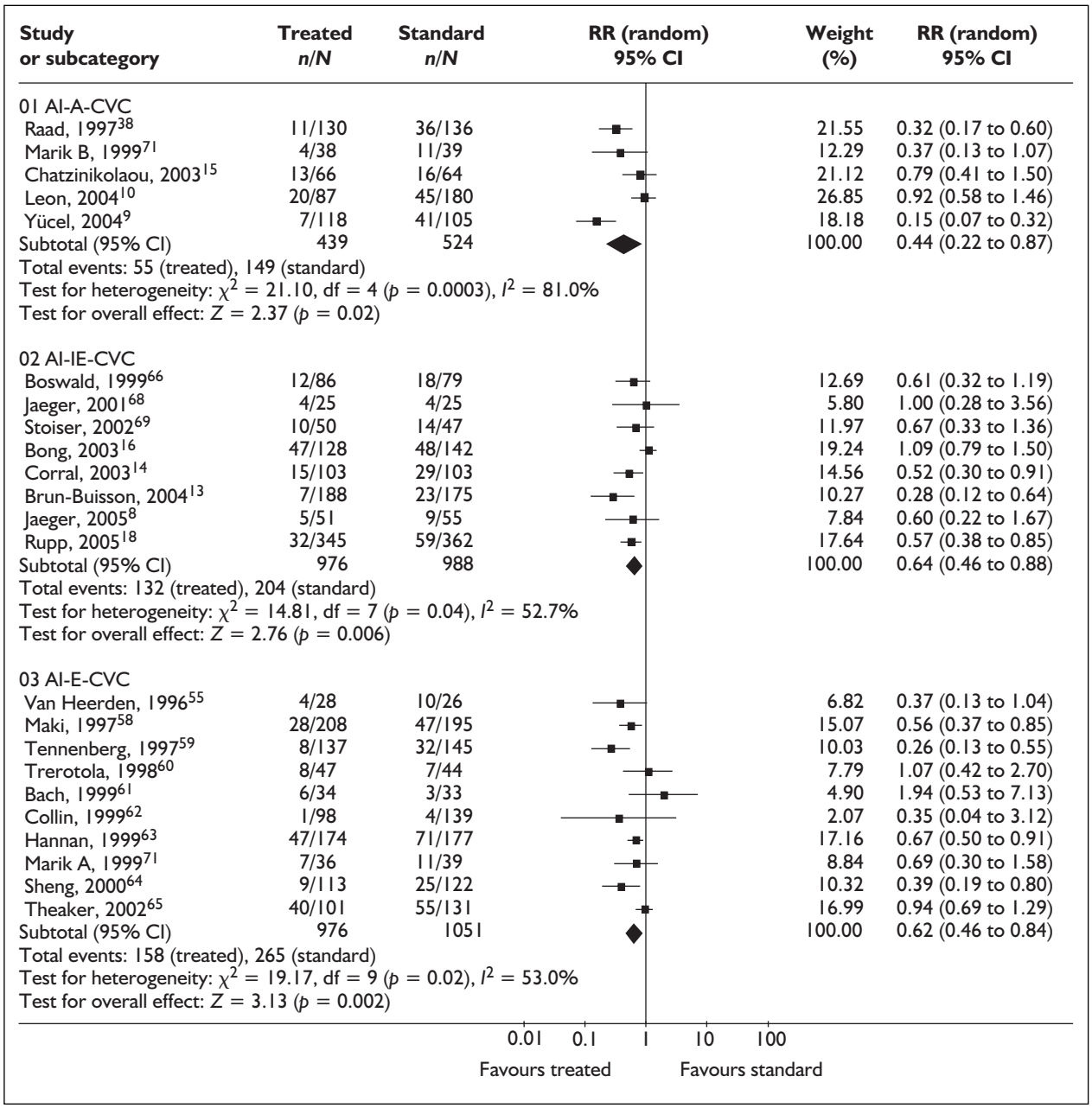

FIGURE 6 *Colonisation rates, subgrouped by category of treatment*

Local clinical signs only

Only one study compared an AI-A-CVC with a standard catheter. The direction of effect favoured the standard CVC, but the result did not achieve statistical significance. Two studies compared an AI-IE-CVC with a standard catheter and although the direction of effect favoured the treated CVC, the result was not statistically significant. Three studies compared an AI-E-CVC with a standard; again, the direction of effect favoured the treated CVC, with the result not achieving statistical significance (*Figure 7*).

Different types of treated CVC

CRBSI

The number of studies for each subgroup varied from one to nine. In all studies, the direction of treatment effects favoured the treated catheter. Subgroups with more than one study achieved statistical significance for all but one subgroup (CHSS AI-E-CVC). Subgroups with only one study had wide and uninformative confidence interval widths (*Figure 8*).

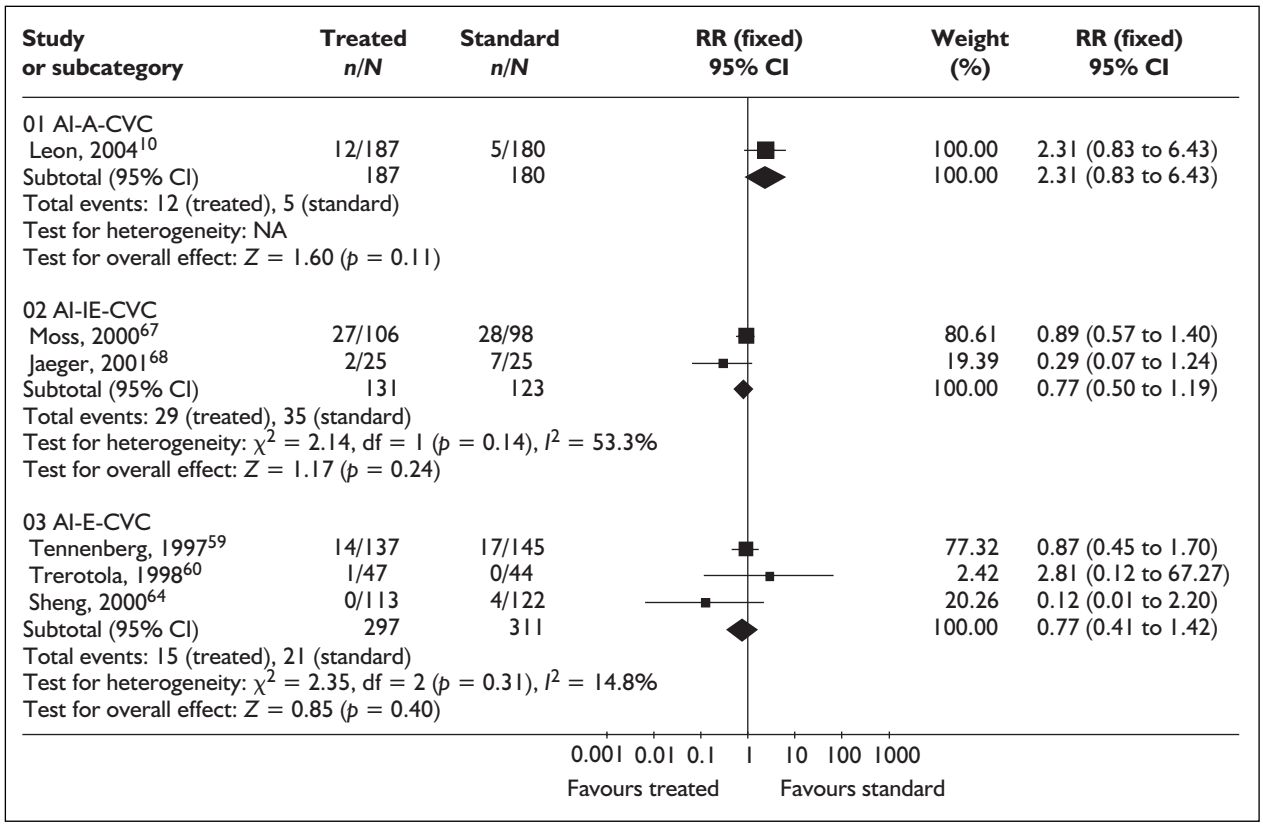

FIGURE 7 *Local clinical signs only rates, subgrouped by category of treatment*

Colonisation

A statistically significant difference was shown for minocycline rifampin, miconazole and rifampicin, CHSS Plus and CHSS catheters. The treatment effects were strong and indicated a large reduction in colonisation. Moderate heterogeneity was evident, so a random-effects model was used (*Figure 9*).

Different classifications of laboratory methods for CRBSI

CRBSI

The number of studies per subgroup ranged from one to 13. Treatment effect estimates for each subgroup indicate a reduced risk of CRBSI; αS+, βS+ and βS– were statistically significant (*Figure 10*). Although the estimate for αS– was non-significant, this may be due to a lack of power as this subgroup contains only one trial.

Different methods of detection of colonisation

The colonisation categories A, C and A or C have strong treatment effects and are statistically significant, indicating a reduction in colonisation for treated catheters (*Figure 11*).

Duration

CRBSI

There was a strong treatment effect favouring treated catheters for 5–12 days (16 studies) and long term (one study) (*Figure 12*).

Colonisation

Only 5–12 days produced a strong and significant treatment effect, with a narrow confidence interval; however, this subgroup contained 17 of the 23 studies. Heterogeneity was detected, so a random-effects method was used (*Figure 13*).

Insertion site

CRBSI

The subgroups femoral, jugular and mixed were statistically significant, favouring the treated CVCs. The subclavian subgroup did not produce a statistically significant result and the confidence interval contained clinically important values in both directions (*Figure 14*). It should be noted that

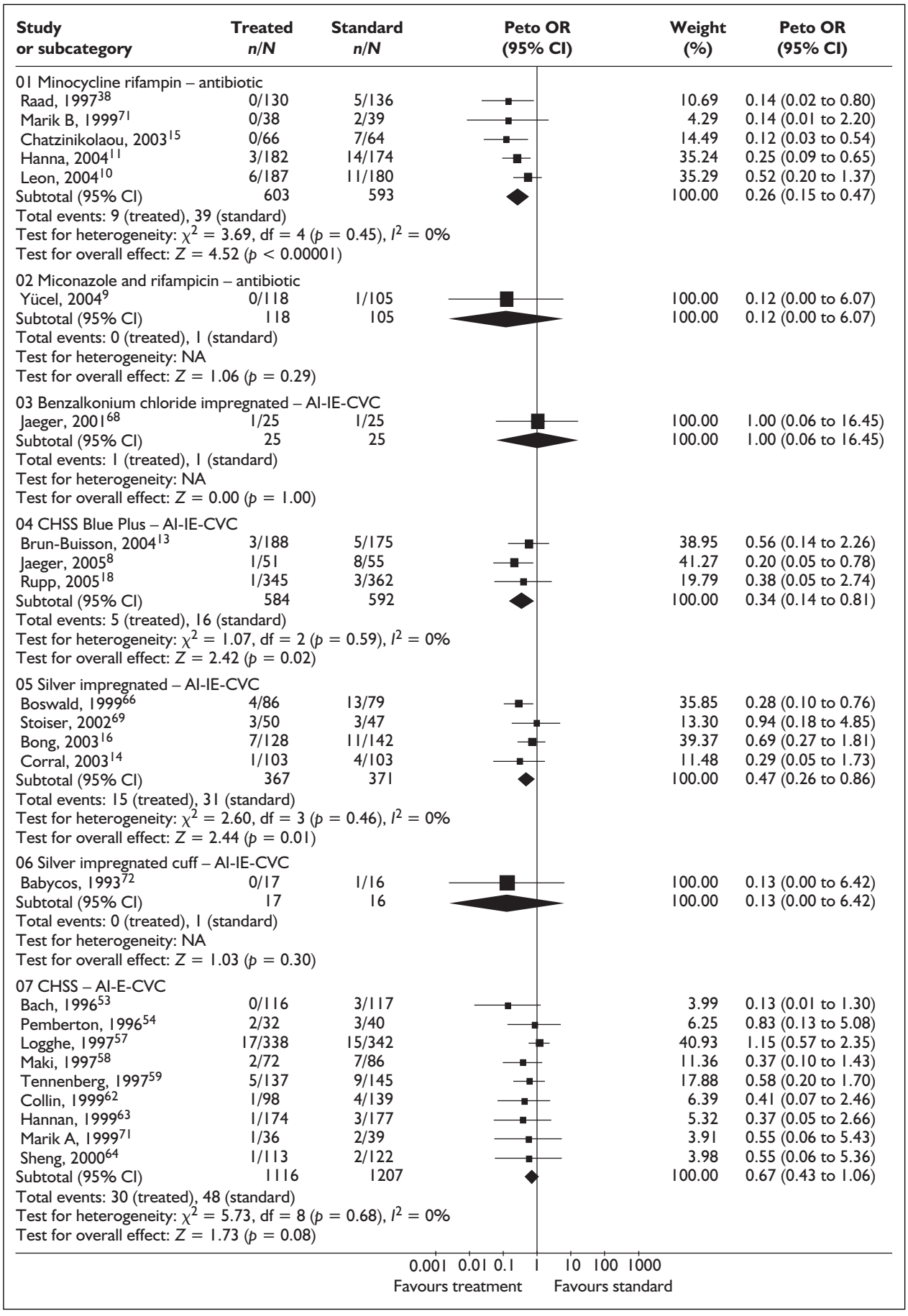

FIGURE 8 *CRBSI rates, subgrouped by different CVCs*

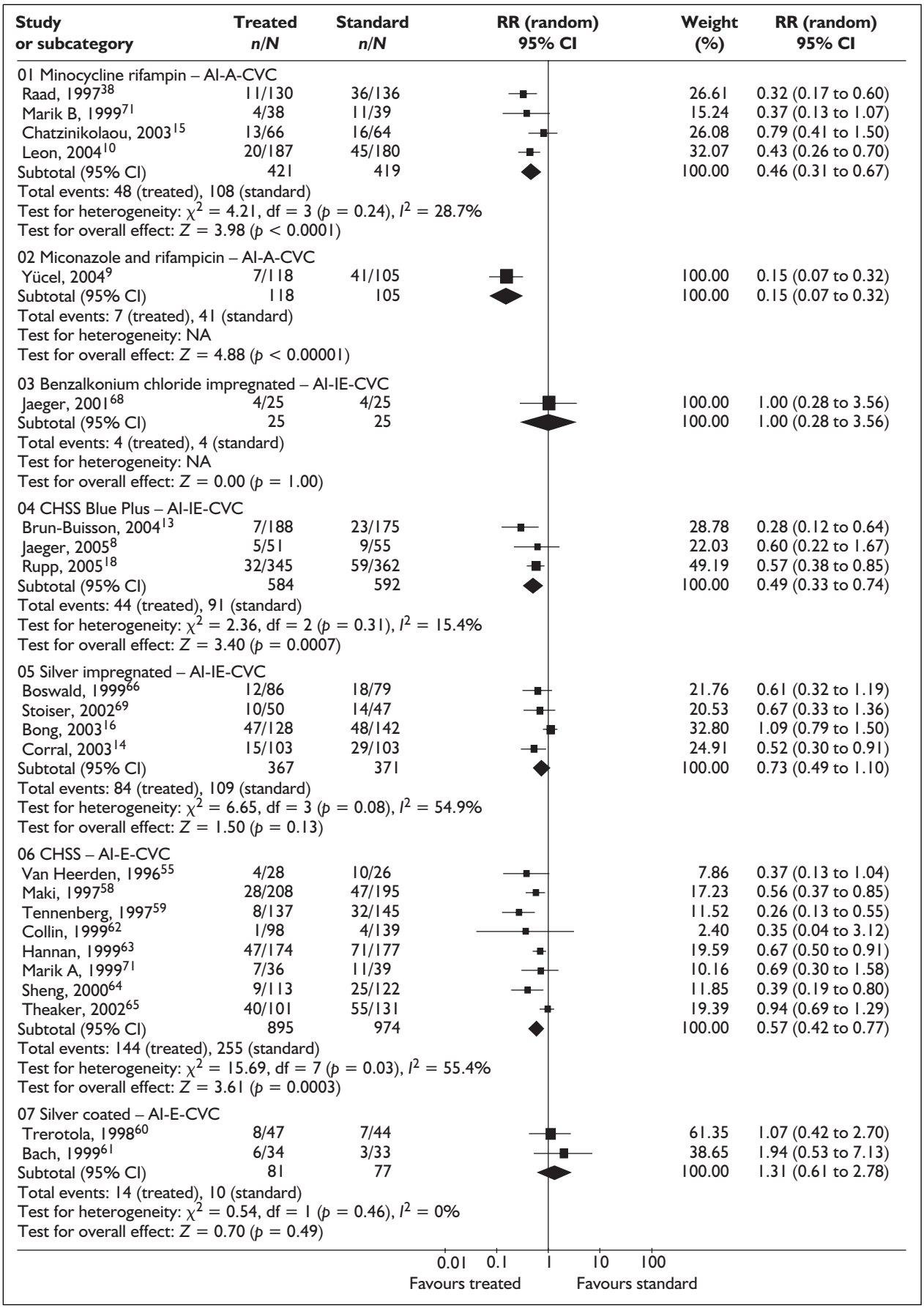

FIGURE 9 *Colonisation rates, subgrouped by different CVC*

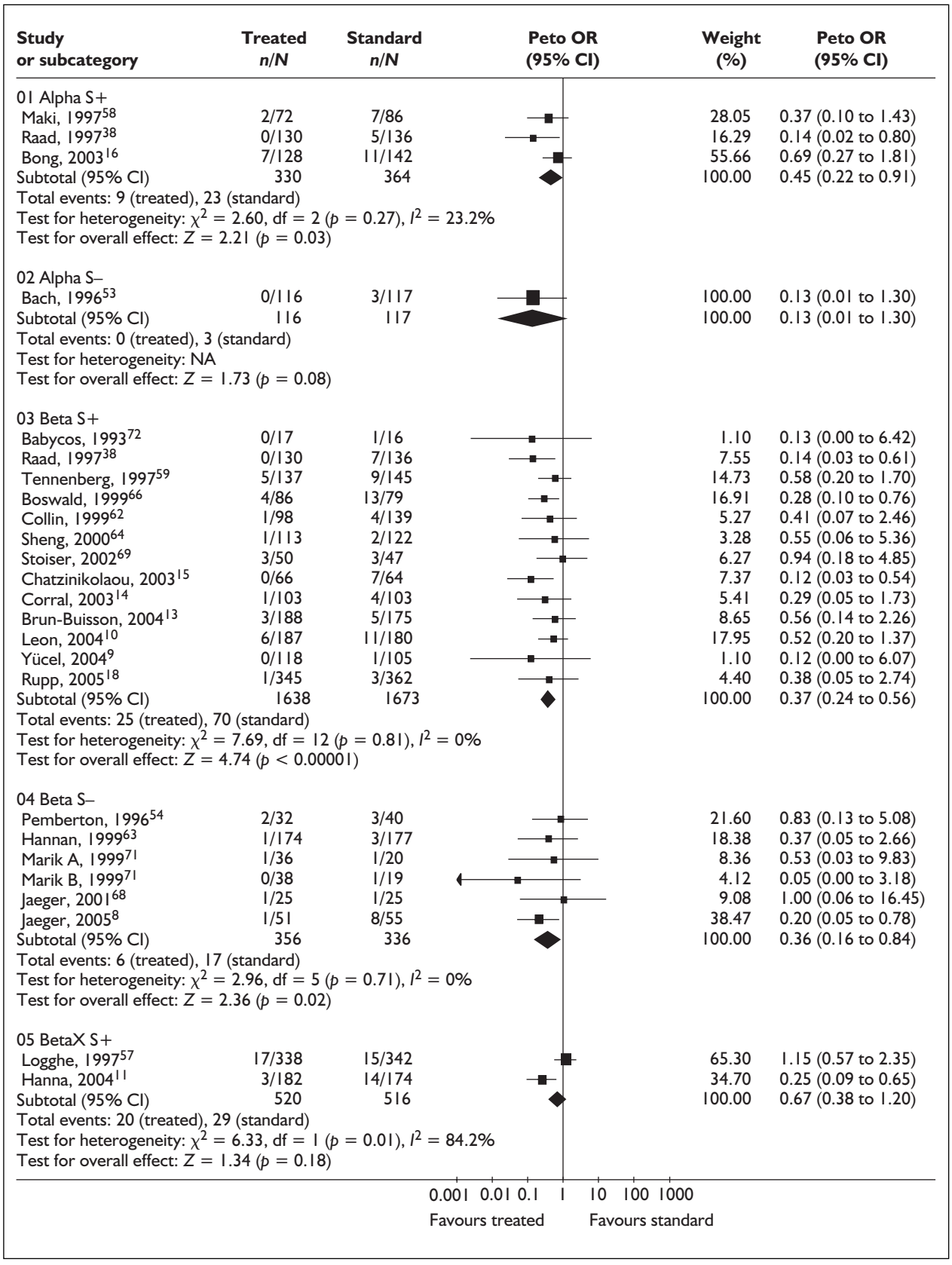

FIGURE 10 *CRBSI rates, subgrouped by classifications of laboratory methods*

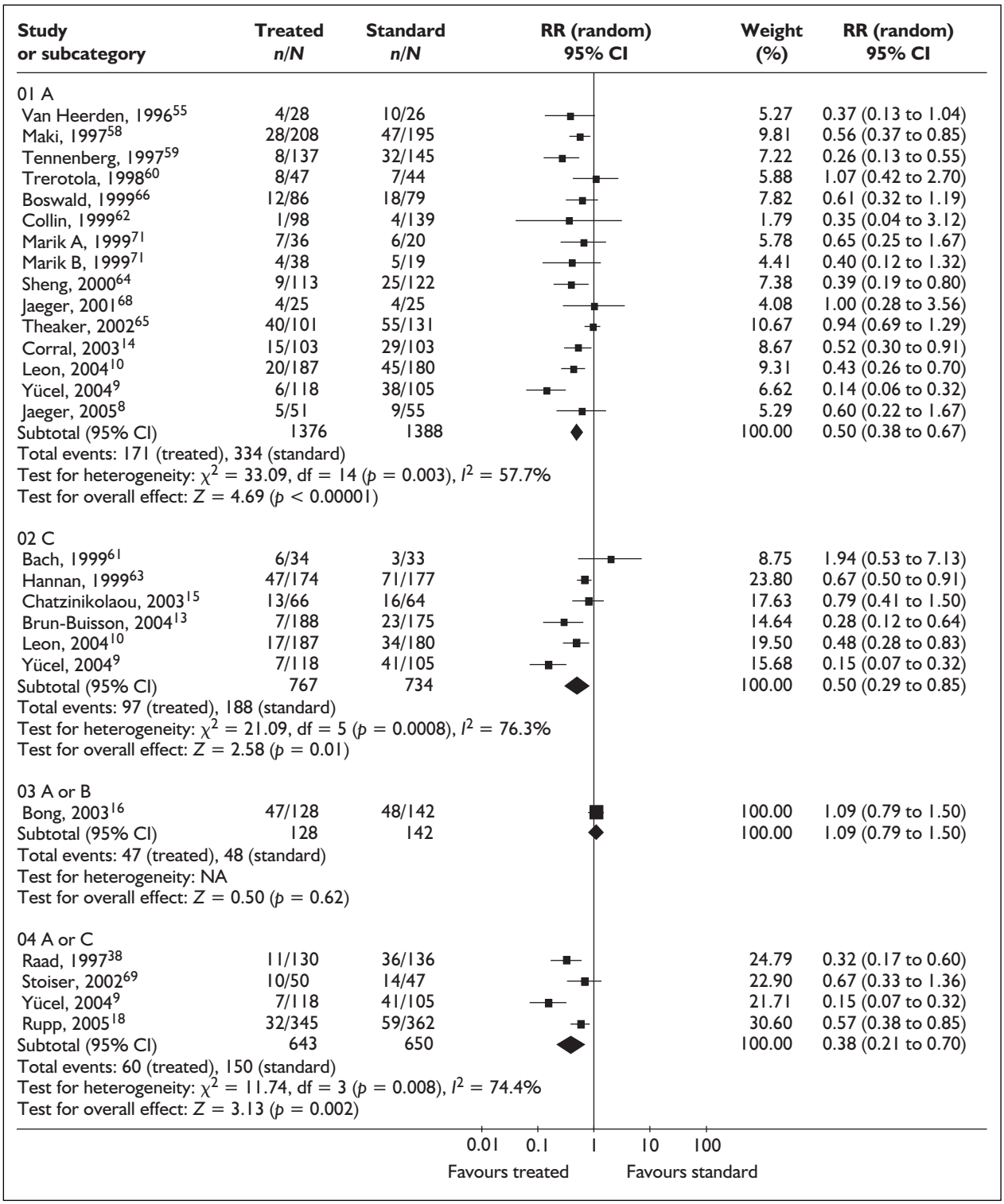

FIGURE 11 *Colonisation rates, subgrouped by different methods of detection*

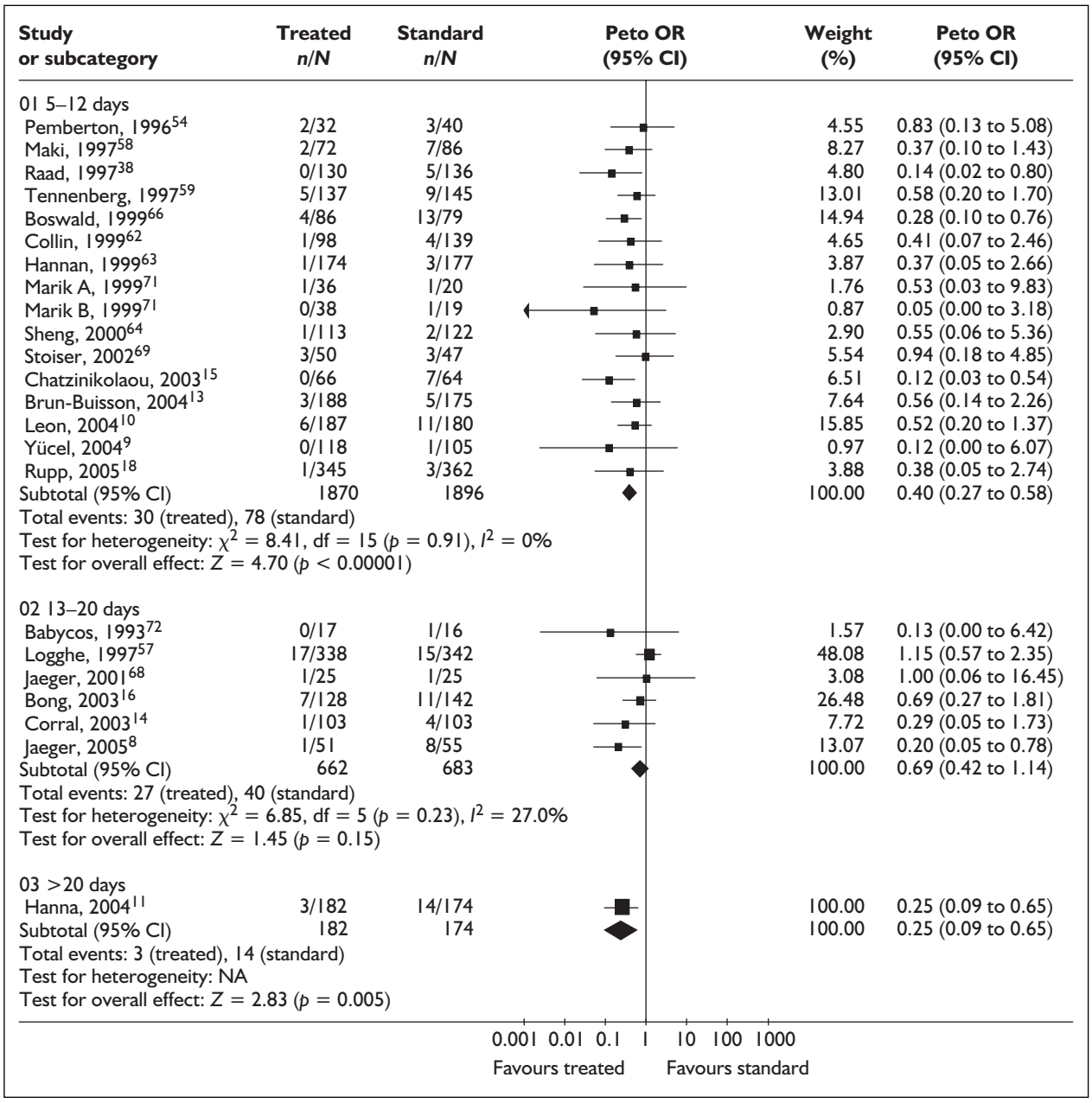

FIGURE 12 *CRBSI rates, subgrouped by duration. Four trials reported median duration: Bong, 2003,[16] Boswald, 1999,[66] Raad, 1997[38] and Stoiser, 2002;[69] all other trials reported mean duration.*

infection rates in these trials are low and two of the studies in this analysis utilise externally treated catheters that had failed to demonstrate effectiveness. Therefore, this result should be treated with some caution.

Colonisation

The femoral, subclavian and jugular subgroups did not produce a statistically significant result, although there were small numbers of studies in each group: one, two and four respectively. The mixed subgroup, which contained 15 of the 22 studies, produced a statistically significant result with a treatment effect favouring treated CVCs (*Figure 15*).

Sensitivity analyses

Analysis by person or by catheter

A sensitivity analysis was carried out to examine the impact on the results of including studies that analysed the data by CVC rather than by person, without allowing for the non-independence of more than one CVC per person. This sensitivity analysis includes those studies that analysed the

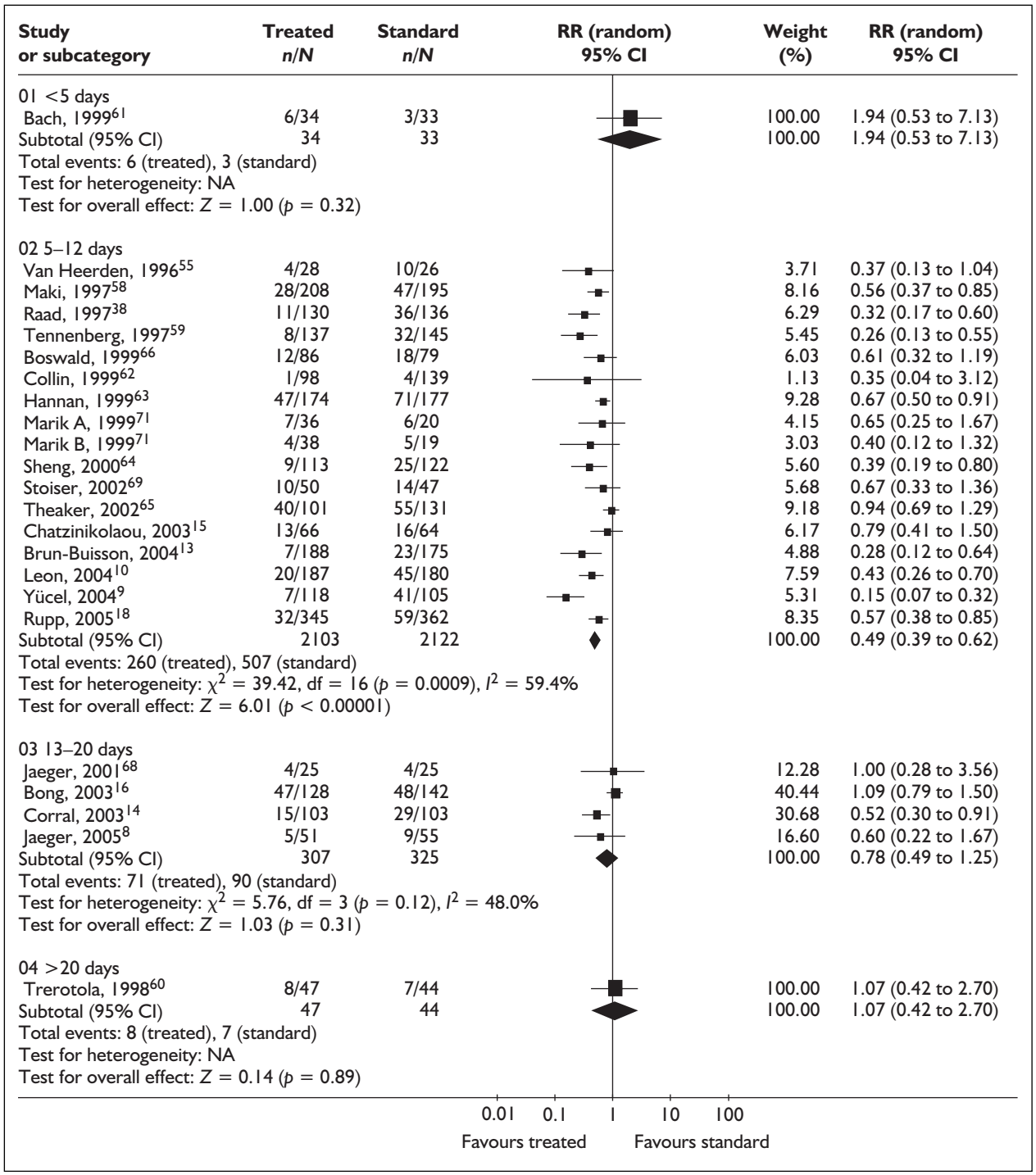

FIGURE 13 *Colonisation rates, subgrouped by duration. Four trials reported median duration: Bong, 2003,[16] Boswald, 1999,[66] Raad, 1997[38] and Stoiser, 2002;[69] all other trials reported mean duration.*

data by patient only. Exclusion of the studies that analysed by CVC did not alter the conclusions for the outcomes CRBSI, colonisation or local clinical signs only (*Figures 16–18*). Formal adjustments for effects of clustering were considered, but it was concluded that this was not worthwhile as not all trials allowed the average cluster size to be calculated. Where this was calculated it was very low, mostly less than two, with one trial having more than three. No estimates of the intracluster correlation coefficient were available, and given the robustness of the results in the sensitivity analysis this was not pursued further.

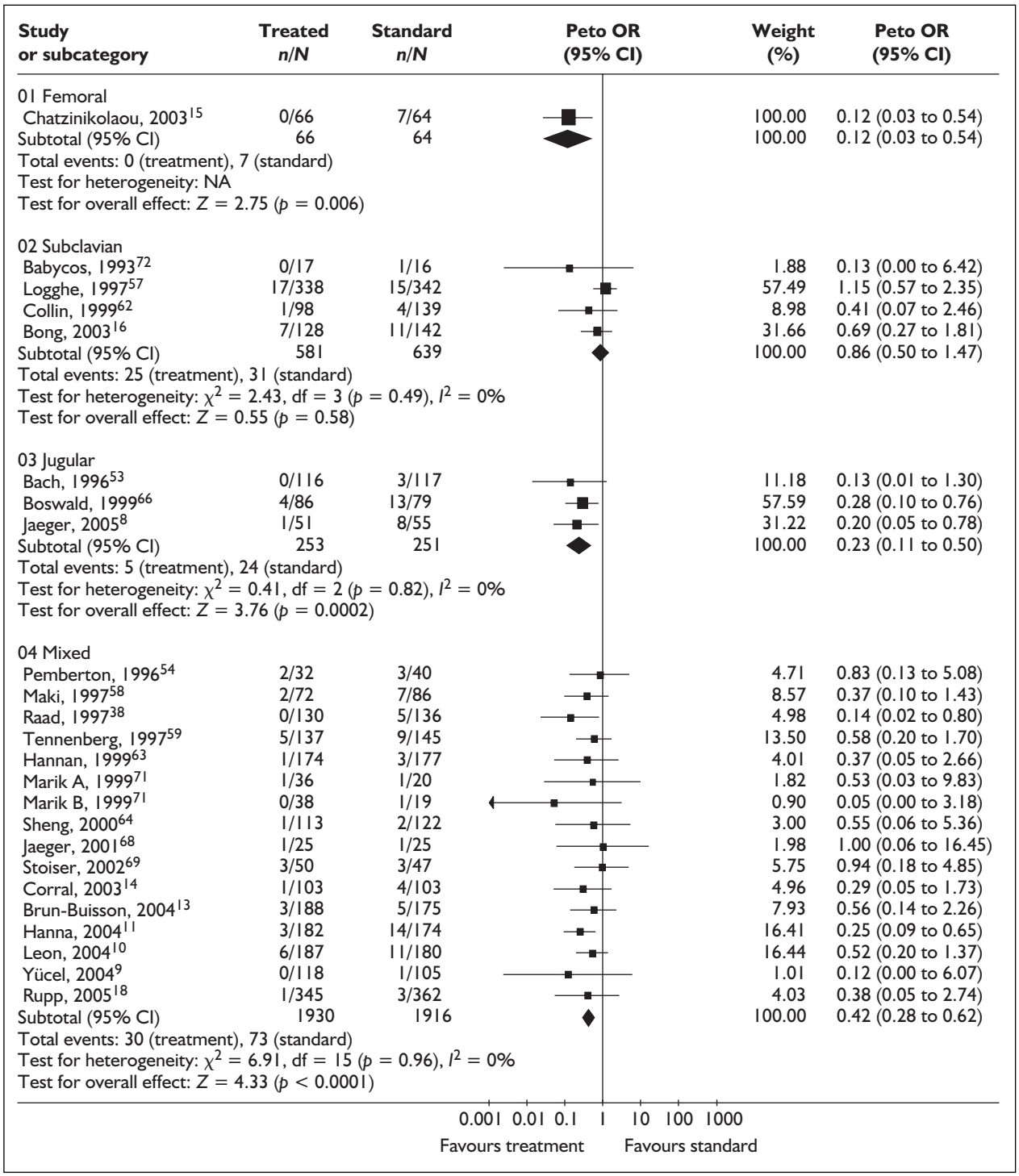

FIGURE 14 *CRBSI rates, subgrouped by insertion site*

Blinding

The impact of including studies with differing designs for blinding was considered for CRBSI and colonisation. The direction and strength of treatment effect were consistent between each group and with the overall pooled result that included all studies (*Figures 19* and *20*).

Randomisation

A sensitivity analysis was carried out for CRBSI and colonisation to consider the impact of including those studies where the method of randomisation was clearly stated compared with those where it was described as randomised, but the method was not described. Although stronger

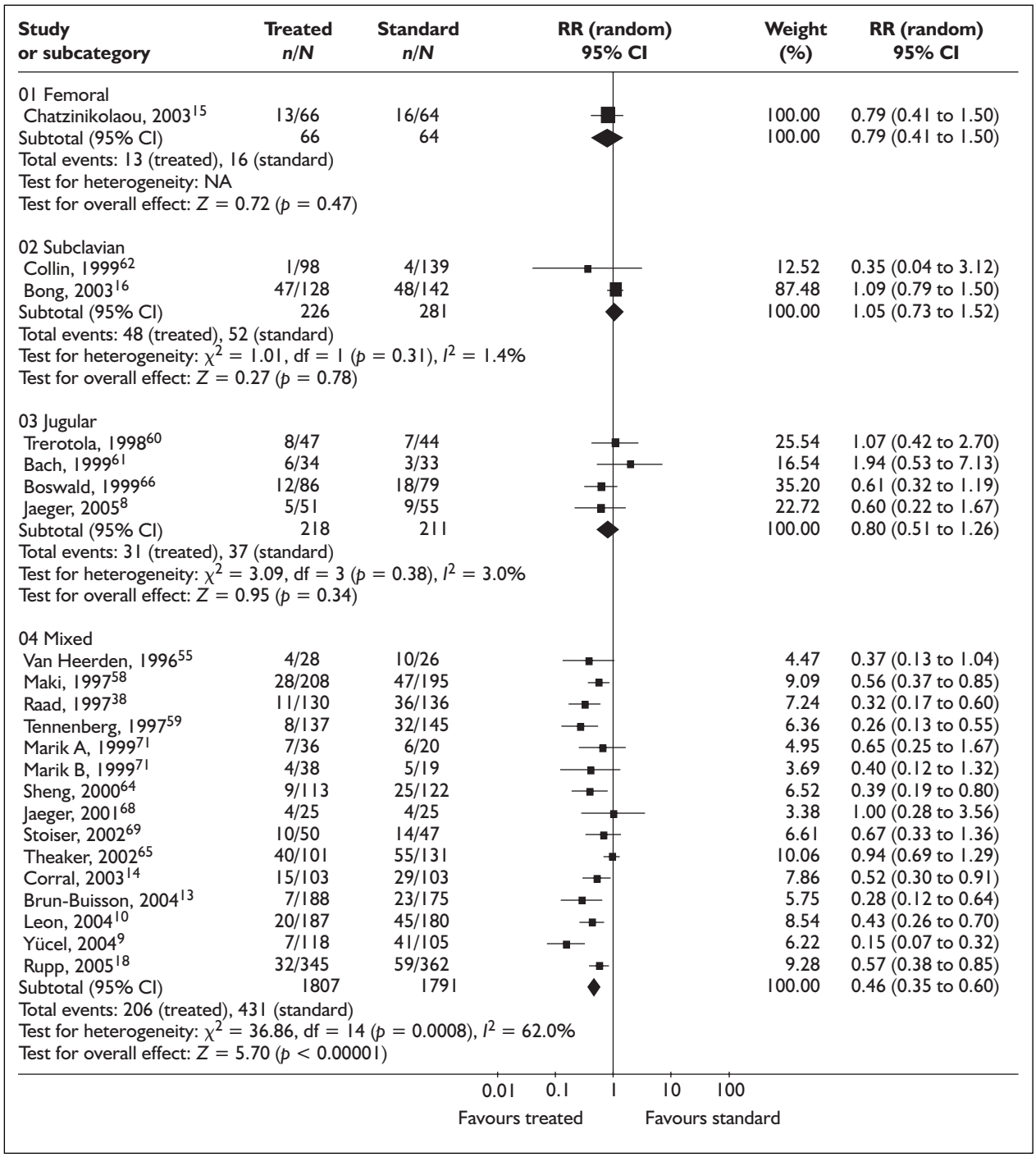

FIGURE 15 *Colonisation rates, subgrouped by insertion site*

treatment effects were seen in both outcomes for those with the randomisation method clearly stated, the results were consistent with the overall pooled result including all studies (*Figures 21* and *22*).

Bias-funnel plots

The interpretation of the funnel plots is subjective and formal statistical tests of asymmetry were not conducted. It is of interest that there are four studies that report colonisation but not CRBSI and five studies that report CRBSI but not colonisation. If CRBSI has been confirmed then colonisation would also have been recorded, but a decision was made not to report it. This may indicate selective reporting of outcomes, which is a form of reporting bias. However, CRBSI is considered to be the most clinically relevant outcome and therefore the decision for a study to report colonisation alone rather than CRBSI may

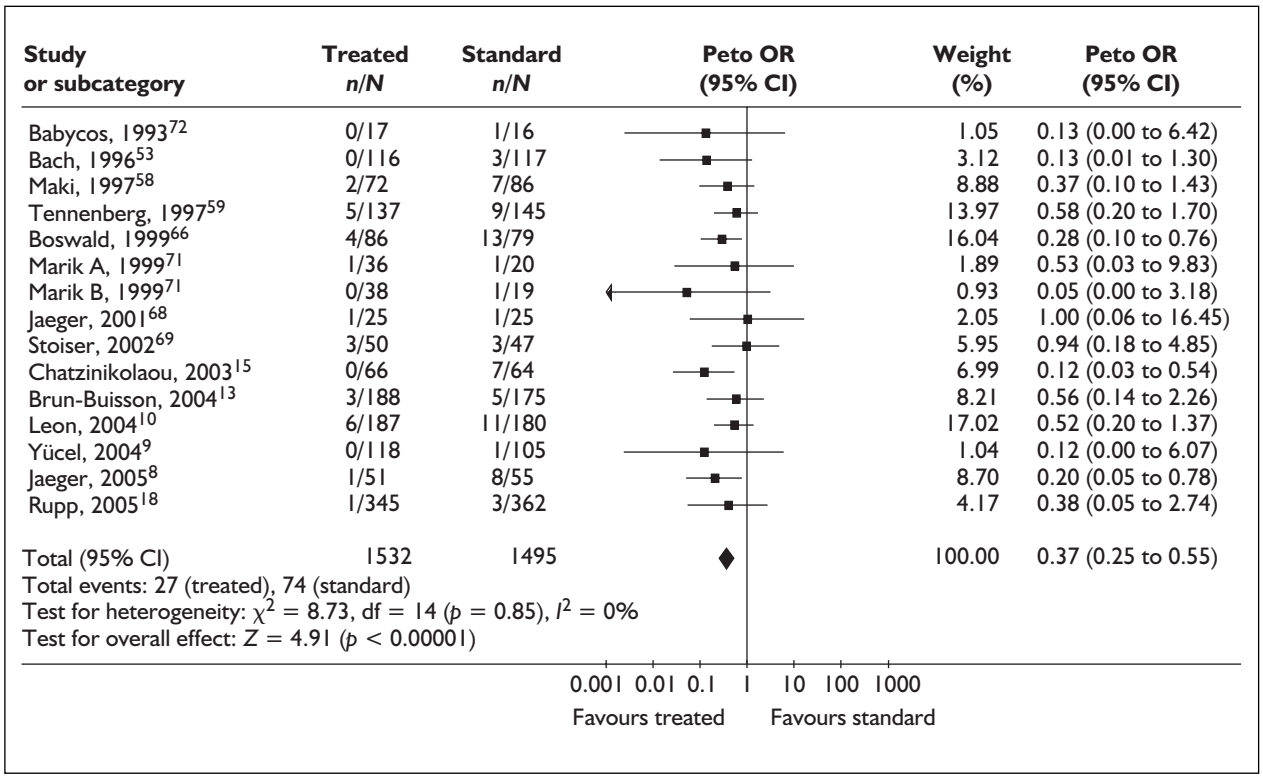

FIGURE 16 *CRBSI: analysis by person*

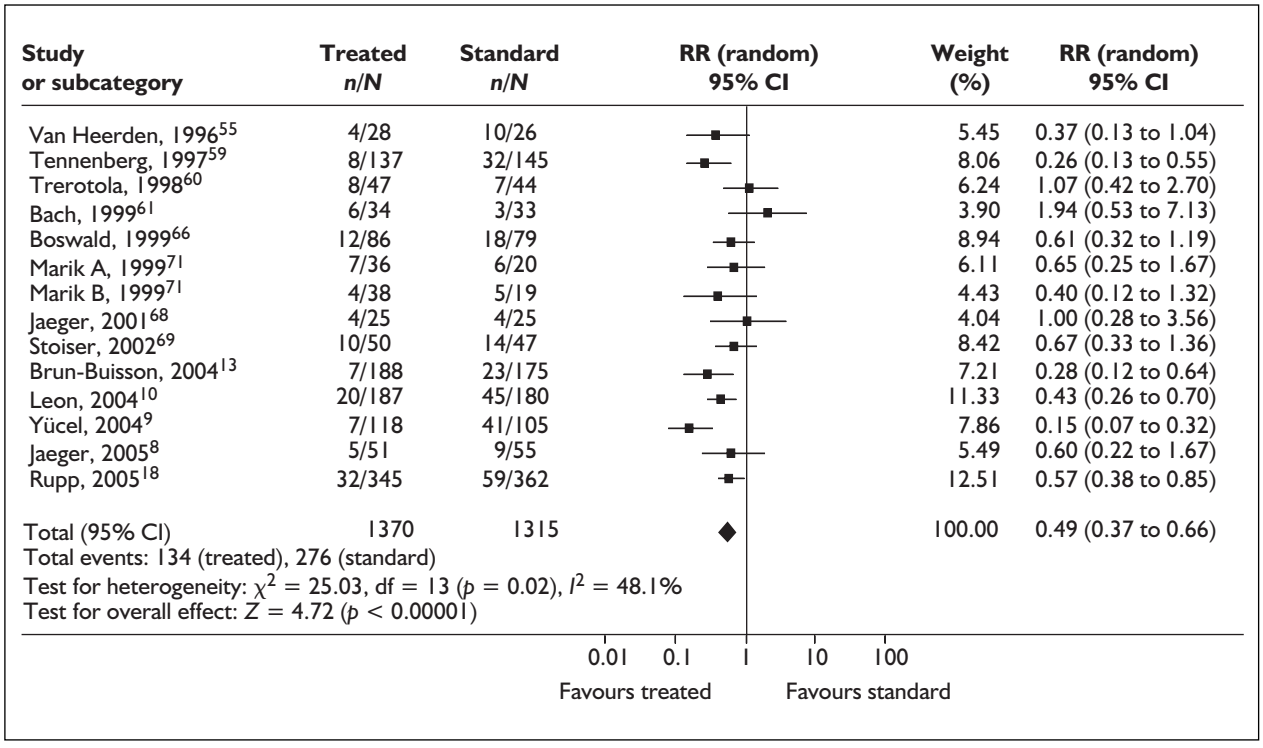

FIGURE 17 *Colonisation: analysis by person*

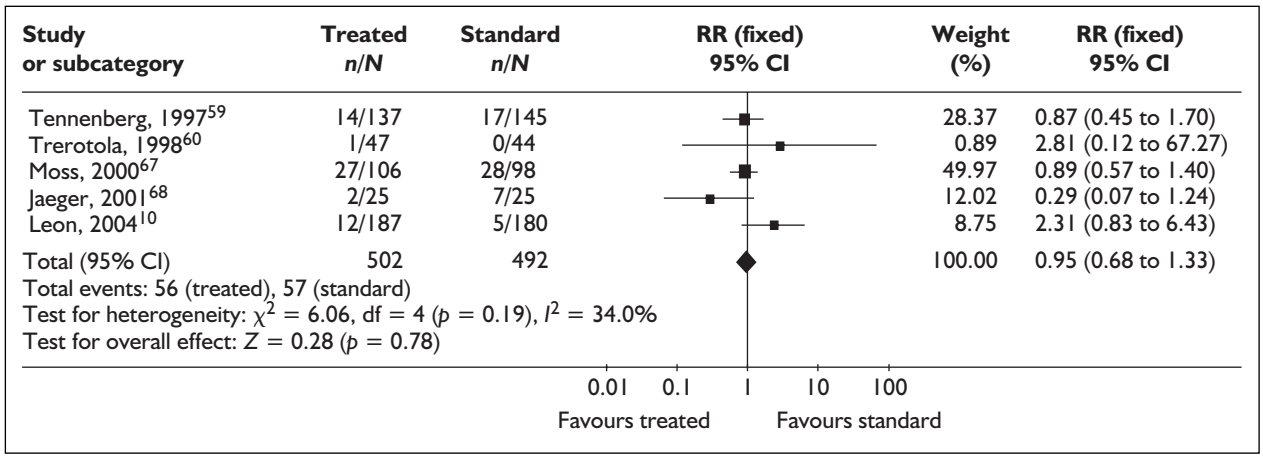

FIGURE 18 *Local clinical signs only: analysis by person*

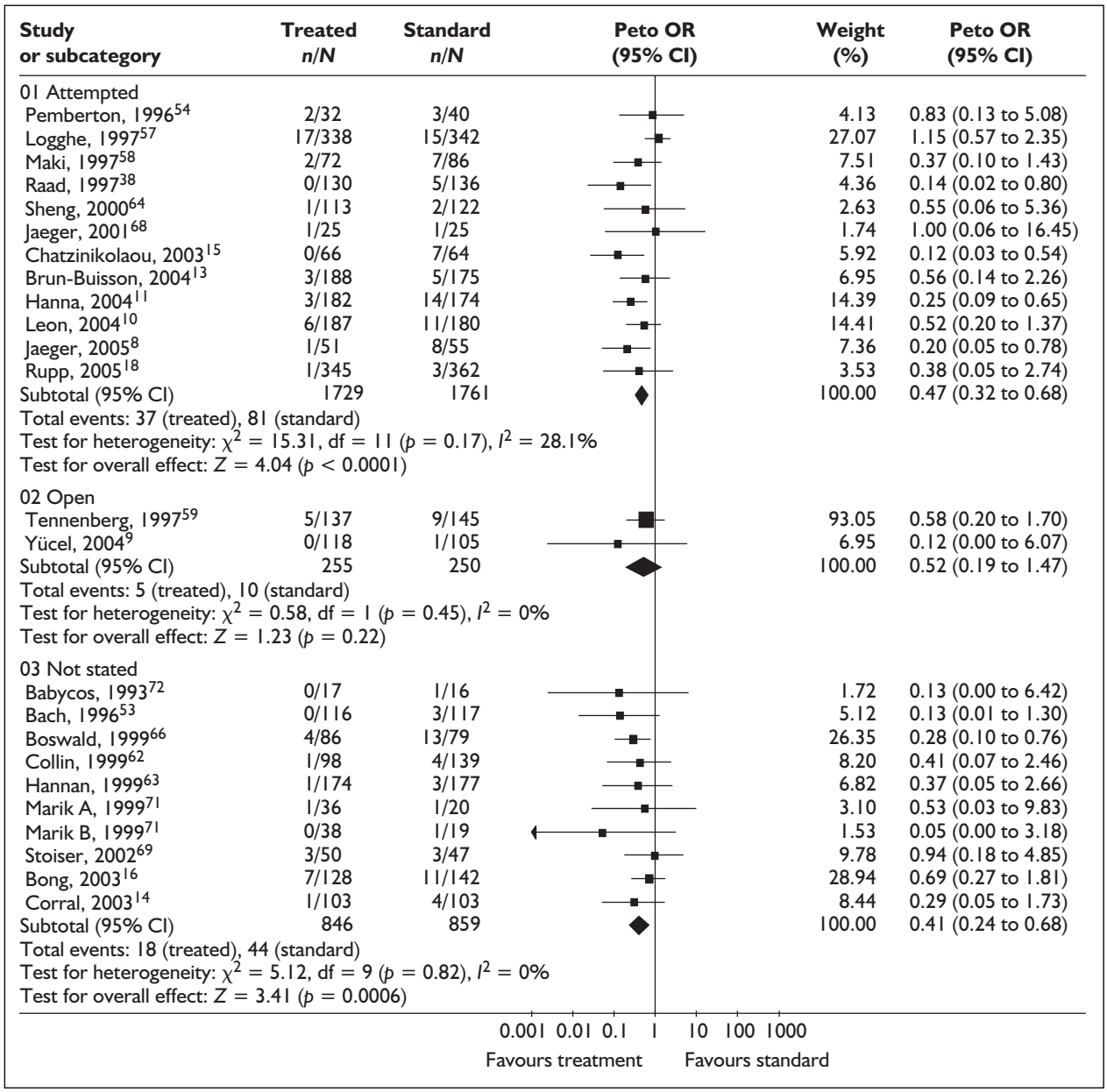

FIGURE 19 *CRBSI: analysis by blinding*

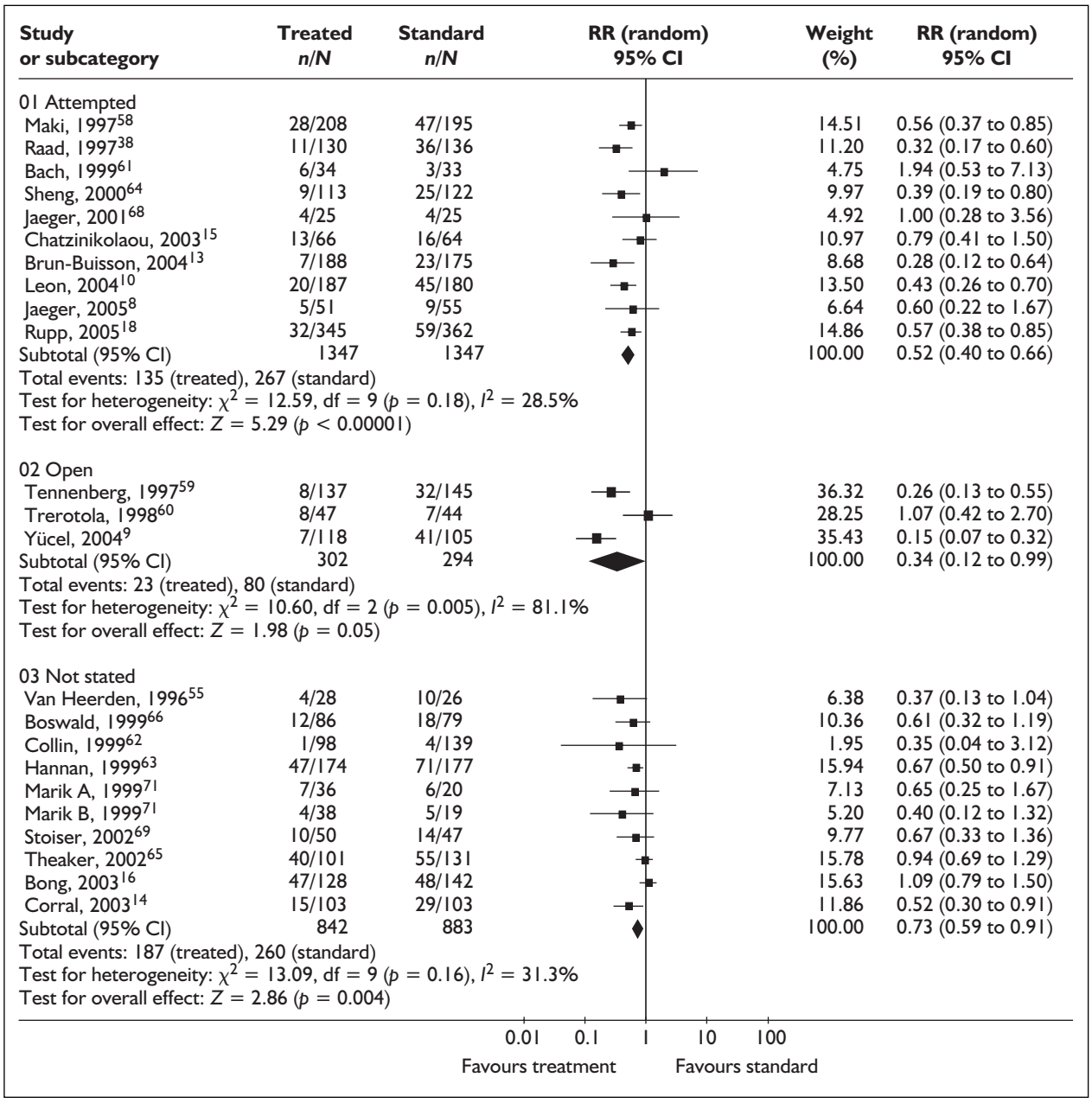

FIGURE 20 *Colonisation: analysis by blinding*

be questionable. Therefore, results should be interpreted with caution as the studies that only report one outcome raise suspicion that outcome selection bias has occurred (*Figures 23* and *24*). However, the studies that reported CRBSI only did not seem to differ in methodological quality or CRBSI findings from those studies that reported both outcomes.

Authors were contacted for these nine studies; no more information was available for three,[11,54,60] no reply was received from four[53,61,65,72] and two authors said that they did not investigate either CRBSI or colonisation.[55,57]

Head-to-head trials

The studies that investigate treated CVCs that are not compared with standard catheters were investigated separately (*Figures 25* and *26*).

CRBSI

Heparin-treated catheters are favoured in comparison to CHSS-treated catheters, but there is no statistically significant difference between the two (OR 0.77, 95% CI 0.17 to 3.45). There is a statistically and clinically significant advantage for MR-treated catheters in comparison to CHSS-treated catheters in reducing CRBSI (OR 0.19,

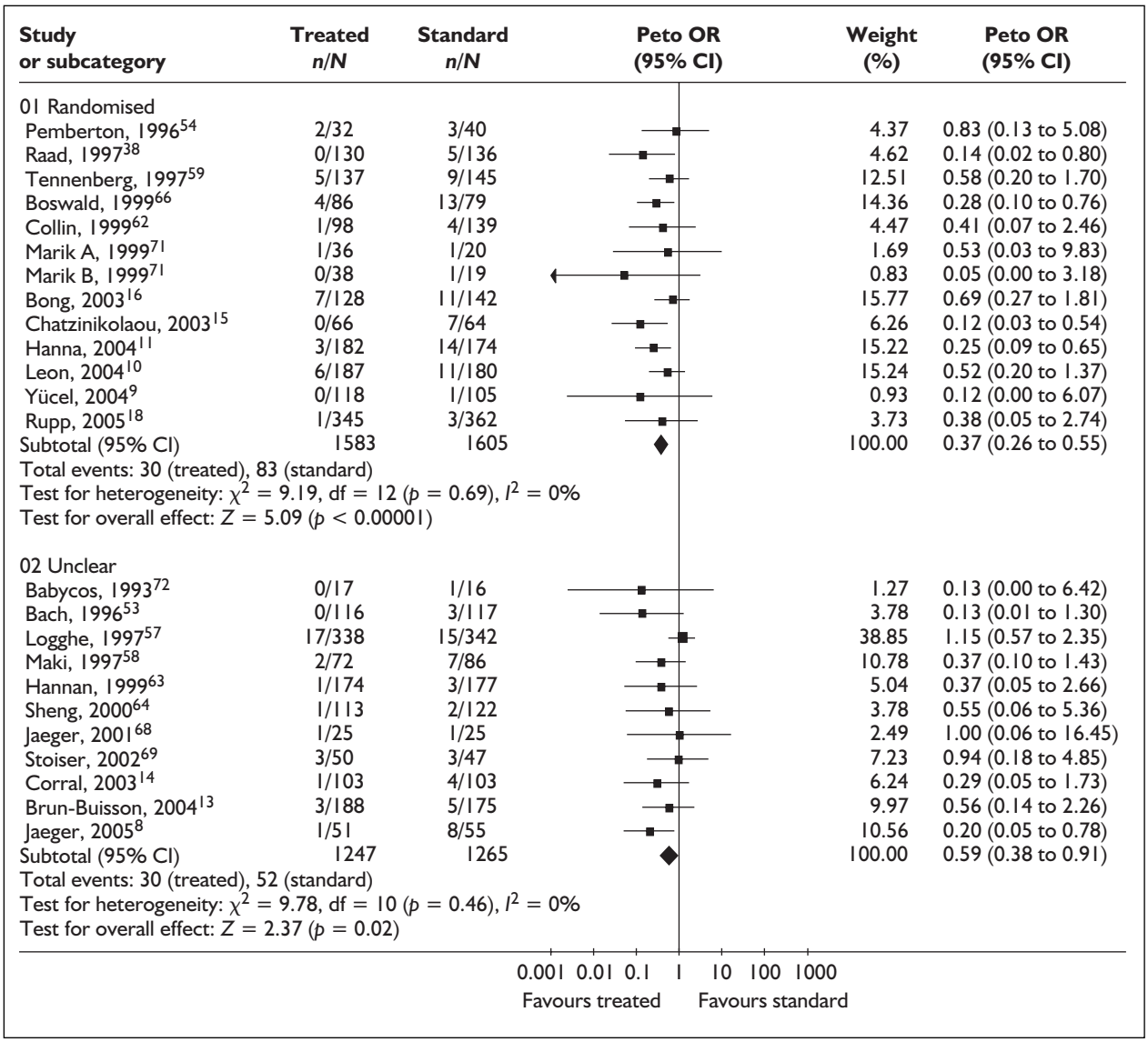

FIGURE 21 *CRBSI: analysis by randomisation*

95% CI 0.07 to 0.54). Benzalkonium chloride-treated catheters are favoured in comparison to silver, carbon and platinum, but there is no statistically significant difference between the two (OR 0.77, 95% CI 0.32 to 1.84). There is a statistically and clinically significant advantage for heparin catheters in comparison to standard catheters in reducing CRBSI (OR 0.15, 95% CI 0.06 to 0.37).

Colonisation

There is a statistically and clinically significant advantage for heparin catheters in comparison to CHSS-treated catheters in reducing colonisation (OR 0.46, 95% CI 0.25 to 0.85). This is also true for MR-treated catheters in comparison to CHSS-treated catheters (OR 0.35, 95% CI 0.23 to 0.52) and benzalkonium chloride-treated catheters in comparison to silver, carbon and platinum-treated catheters (OR 0.61, 95% CI 0.43 to 0.86).

Numbers needed to treat

Using the odds ratios from the CRBSI analysis in the section 'All studies' (p. 39), a range of values for number needed to treat (NNT) was calculated for a selection of control group events found within the meta-analysis. The largest and smallest control group events were used, and several values in between (*Table 13*).

Depending on the value of the control group event, the NNT varied between 13 (95% CI 10 to 17) and 221 (95% CI 184 to 304).

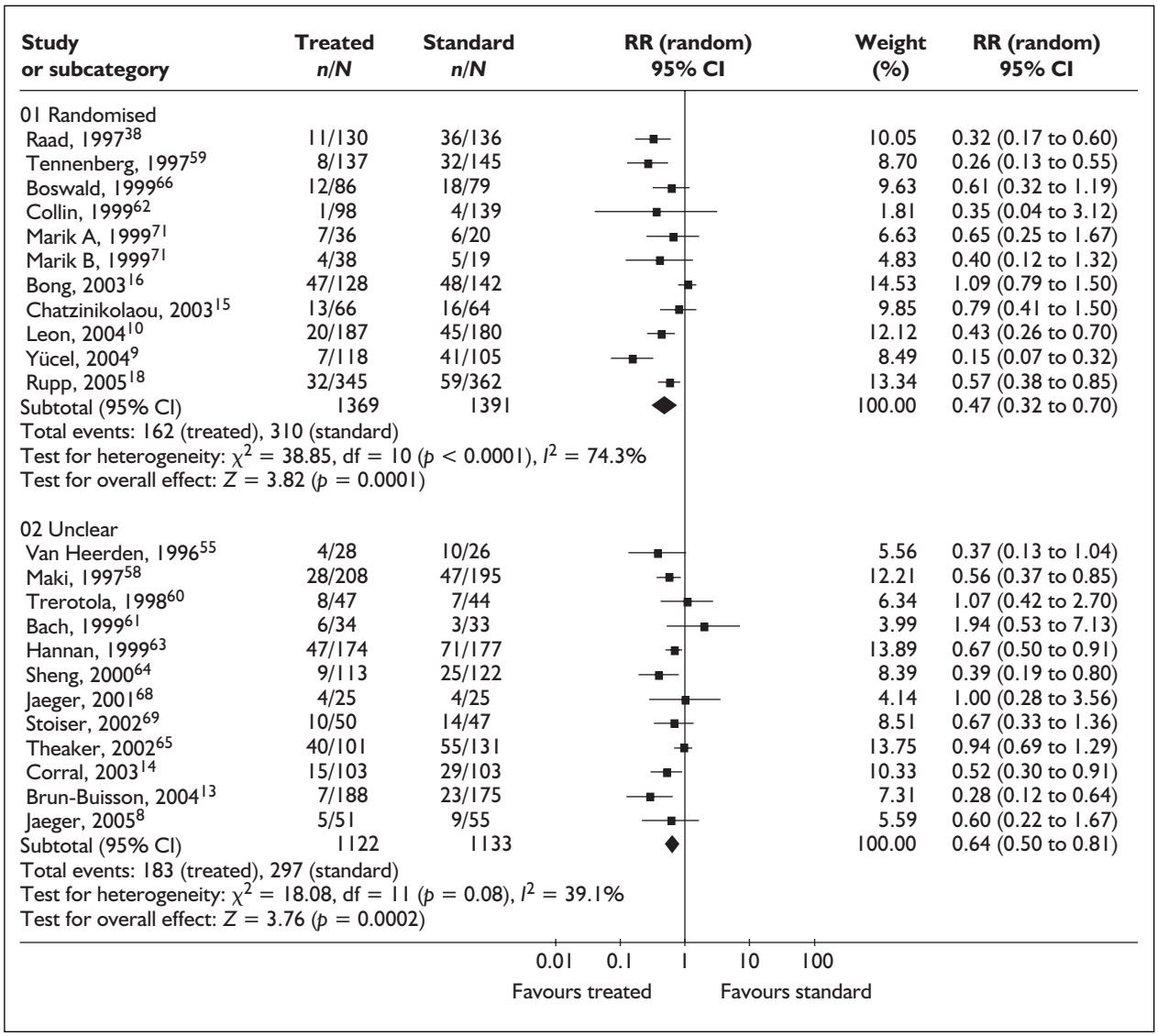

FIGURE 22 *Colonisation: analysis by randomisation*

Summary of results

CRBSI

Rates of CRBSI are reduced if AI-IE-CVCs are used, regardless of whether the treatment coated both the internal and external surfaces of the CVC. This was true regardless of the method of detection used (e.g. α, β, θ).

When the duration of insertion was investigated, an average duration of between 13 and 20 days did not result in a statistically significant treatment effect, but for trials with an average duration of between 5 and 12 days and for the one study that had a mean duration of more than 20 days there was a statistically significant treatment effect. However, the direction of the treatment effect was consistent across all subgroups.

In addition, a treatment effect was observed for both femoral and jugular insertion sites and for those studies including a mix of insertion sites. A significant treatment effect was not observed in trials using subclavian insertion sites, although the direction of effect was the same as in the other subgroups.

Sensitivity analyses were conducted to assess the impact on the results of differences in study design (person or catheter, blinding and randomisation). All results were consistent with the main analysis.

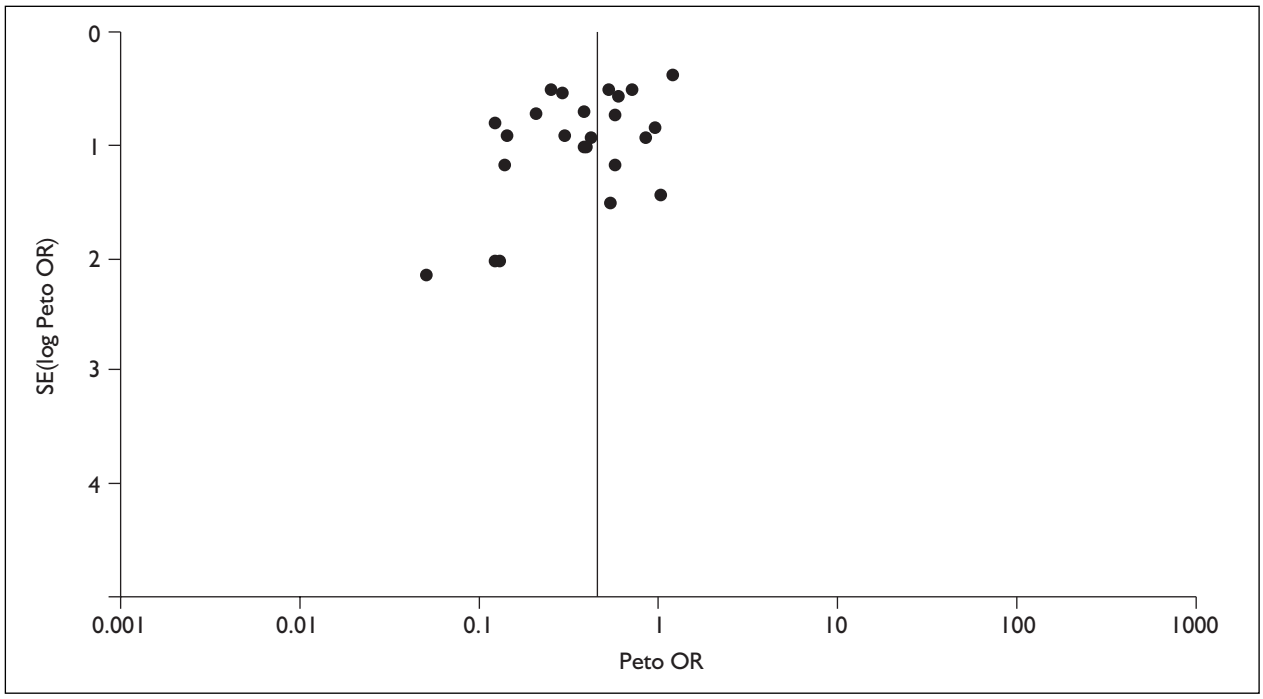

FIGURE 23 *CRBSI: funnel plot showing the odds ratios*

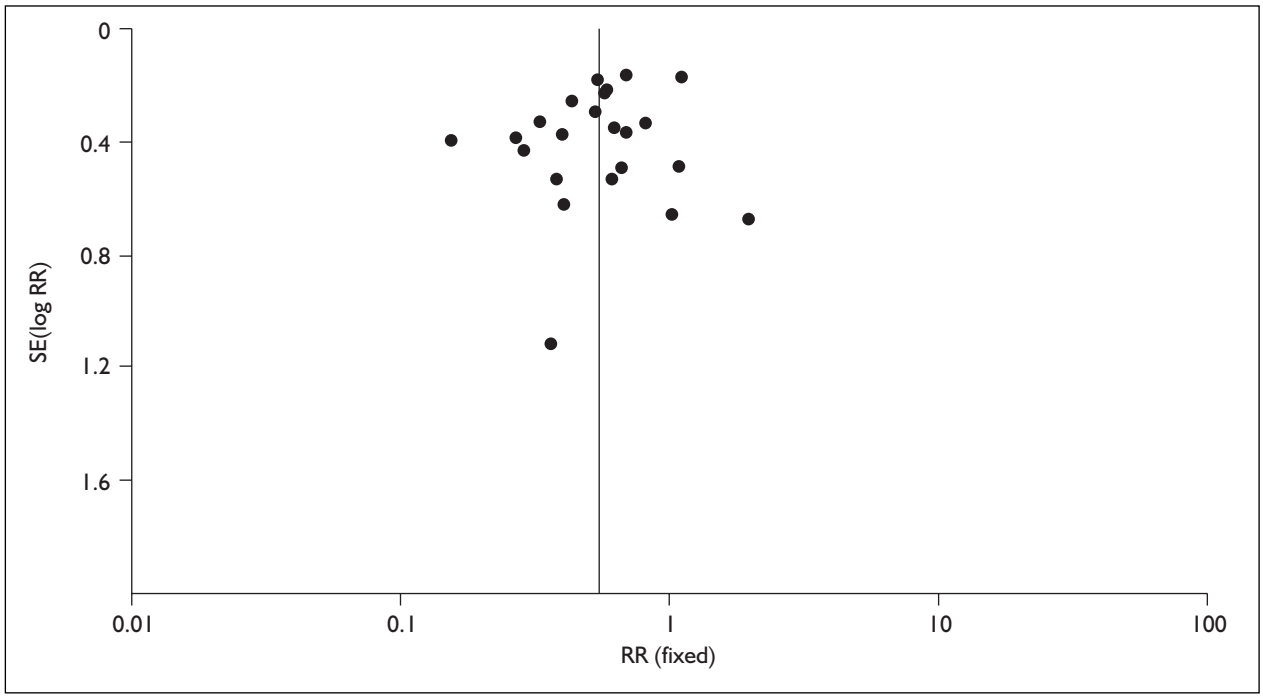

FIGURE 24 *Colonisation: funnel plot showing the relative risk*

One study included a comparison of MR- versus CHSS-treated catheters and reported lower rates of CRBSI in the MR group.

Colonisation

Significant heterogeneity was detected in the meta-analyses colonisation. None of the subgroup and sensitivity analyses conducted could explain the heterogeneity. However, significant treatment effects were found regardless of treatment and whether the internal surface of the CVC was treated or not. The direction of the treatment effect was not altered by the different method of detection used for colonisation, except for one subgroup which only included one study.

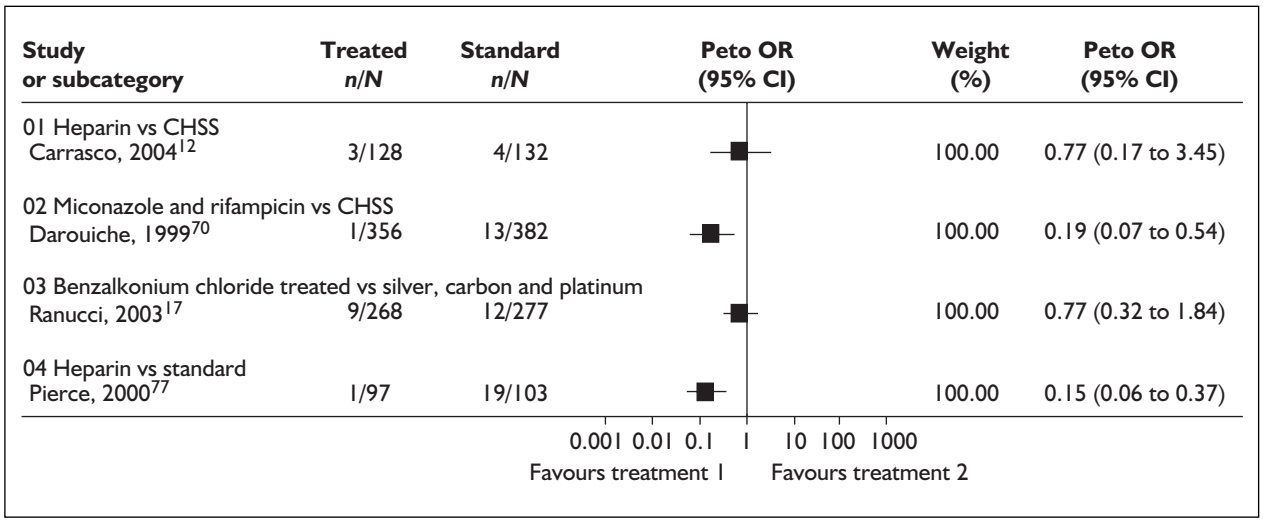

FIGURE 25 *CRBSI: analysis by head-to-head trials. (As Carassco, 2004[12] compares heparin to CHSS, Pierce, 2000[77] is included for completeness as this study compares heparin to standard.)*

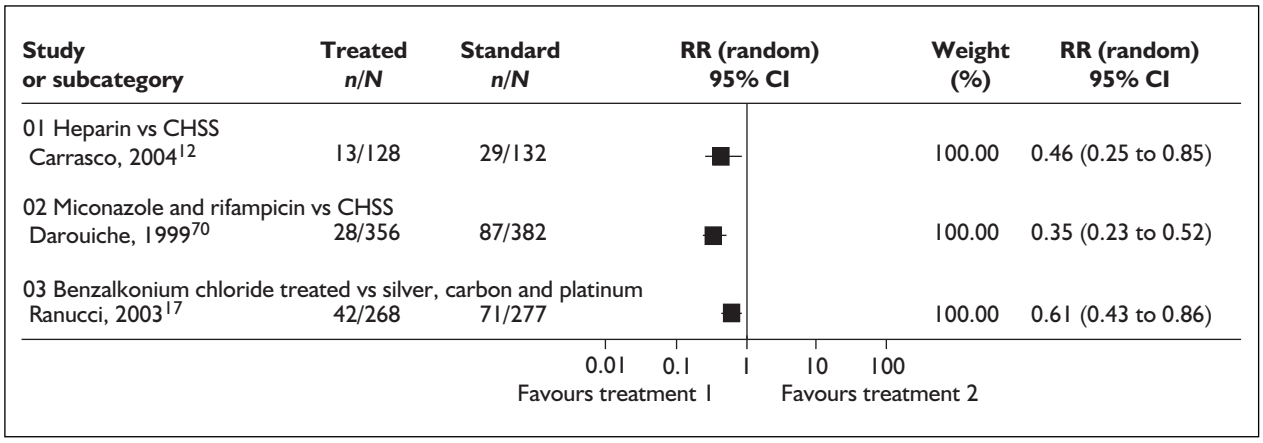

FIGURE 26 *Colonisation: analysis by head-to-head trials*

TABLE 13 *Numbers needed to treat to avoid an occurrence of CRBSI*

Study	Control group event rate	NNT (OR = 0.45)	Lower limit (OR = 0.34)	Upper limit (OR = 0.60)
Rupp, 2005[18]	0.0083	221	184	304
Bach, 1996[53]	0.0256	72	60	100
Marik, 1999[71]	0.0500	38	31	52
Pemberton, 1996[54]	0.0750	26	21	35
Chatzinikolaou, 2003[15]	0.1094	18	15	25
Boswald, 1999[66]	0.1646	13	10	17

There was only a significant treatment effect for studies with an average duration of insertion of between 5 and 12 days. The direction of the treatment effect was the same for the subgroup 13–20 days. The other two subgroups contained only one study.

There was a significant treatment effect for studies using a mixture of insertion sites, and for individual sites the results were not statistically significant. A small number of studies was included in each group.

As with CRBSI, the sensitivity analyses indicated that the differences in study design had no impact on the results. The results were consistent with the main analysis, showing a significant treatment effect.

Clinical signs and symptoms and local clinical signs only

For the analyses involving these two outcome categories there were too few studies to produce meaningful results.

Numbers needed to treat

Depending on the value of the control group event the number of patients needed to treat to prevent a CRBSI varied between 13 (95% CI 10 to 17) and 221 (95% CI 184 to 304).

Clinical discussion

The results of the principal meta-analysis demonstrate a significant decrease in the rates of CRBSI when AI-CVCs are compared with standard CVCs. On closer examination, subgroup analysis reveals that there is a significant decrease in the rates of CRBSI when AI-IE-CVCs (CHSS Plus, silver impregnated and benzalkonium chloride impregnated) and AI-A-CVCs (MR and miconazole and rifampicin) are used instead of standard CVCs. This is not the case for AI-E-CVCs (CHSS and silver). However, the internally and externally treated CHSS Plus catheter, evaluated in three studies in the current review, is not yet available in the UK as it is currently awaiting Conformité Européene (CE) marking; it is likely that this second generation catheter will eventually replace the externally treated CHSS catheter.

Several factors influence the clinical effectiveness of AI-CVCs to reduce CRBSI. These include study design factors, diagnosis of CRBSI, patient population and practice characteristics.

The quality of the included studies varied. Almost half of the studies failed to report true randomisation methods and more than half failed to achieve concealment of allocation. The number of CVCs allowed per patient varied across studies, with almost half allowing more than one CVC per patient, making data analysis complex and limiting the ability to carry out ITT analysis. The majority of included studies did not blind the outcome assessors. Using sensitivity analysis, the effects of randomisation and blinding methods were investigated, as well as analyses by catheter or patient. The results of the meta-analyses remained unchanged.

Two-thirds of the studies included were commercially funded and a further 11 trials failed to mention where funding was obtained from. The funding of trials by industry has been shown to increase the likelihood of finding a positive result,[78,79] thereby raising the question of bias in these trials.

Within the included trials a wide variety of methods was used to define and diagnose CRBSI (peripheral versus CVC samples, molecular fingerprinting and variations in cut-off points related to diagnosing positive cultures), which therefore limited comparability across studies. However, for the purpose of this review the different measures and definitions were categorised and a subgroup analysis determined that the treatment effect size was consistent across all definitions.

In six trials no measure of CRBSI was reported. Rates of colonisation or local clinical signs of infection were used as the primary outcomes. These measures are surrogate indicators of the clinical effectiveness of the catheters in preventing CRBSI; colonisation on its own may simply reflect contamination of the catheter by entry-site flora during removal. This is likely to be the case in studies where the rates of colonisation are considerably higher than the rates of CRBSI; for example, Hannan,[63] where the standard rate of CRBSI is 2%, but their standard rate of colonisation was 40%, and Yücel[9] (CRBSI = 1%, colonisation = 36–39%). This contamination may explain the heterogeneity of the reported rates of colonisation.

As discussed earlier, the risk of CRBSI depends on patient population factors such as age, neutropenia and presence of distant infection. Although the studies reported some of these key variables, there was such inconsistency across studies that meaningful subgroup analyses were not possible. Therefore, definitions of high-risk populations that would be most likely to benefit from the use of AI-CVCs were not possible.

In the 32 included trials CRBSI rates ranged between less than 1%[18] and 16%[66] for standard CVCs, and from 0%[9,15,18,38,53] to 6%[69] for AI-CVCs. In two trials[9,18] the control arms reported CRBSI rates of 0.83% and 0.95%, confirming that low rates of infection are possible without recourse to the use of AI-CVCs. However, there may be

situations where either good practice is unavoidably compromised or there are specific patient risk factors (e.g. third degree burns at the insertion site, or conditions that render patients less able to fight infection).

Ideally, a subgroup analysis of the effect of good practice would have been conducted as part of the review. However, because of a wide range of practice characteristics that differ across time and country, and the often poor reporting of techniques and the subjectivity of grouping 'good practice' versus 'poor practice', such a subgroup analysis was not possible. As all trials were RCTs, it might be assumed that practice techniques were comparable across arms of each trial and that any differences between infection rates within trials were not the result of differences in clinical practice. This does not, however, preclude the possibility that differences in infection rates between trials may be related to differences in clinical practice. Where CRBSI is a rare event (possibly indicative of good clinical practice) it would be difficult to power studies sufficiently to show a treatment effect, and this may explain studies not showing such an effect.

In the review, it was possible to address two aspects of clinical practice that are risk factors for CRBSI: duration of catheter *in situ* and site of insertion.

Duration

The analysis of CRBSI rates at 5–12 days includes 16 studies using a mix of catheters and demonstrated clinical effectiveness. Where catheterisation is planned to be greater than 12 days then the results of this review may suggest that an AI-CVC does not significantly reduce the rates of CRBSI or colonisation. The analysis of data for 13–20 days included six studies and failed to demonstrate effectiveness. The largest study in this group, by Logghe and colleagues,[57] assessed the effectiveness of the externally treated CHSS catheter and failed to demonstrate effectiveness. The one study of greater than 20 days did show a significant reduction in the rate of CRBSI.[11]

Site of insertion

The descriptive epidemiology of CRBSI rates is that they are highest in femoral veins and lowest in subclavian veins. Subgroup analyses showed that AI-CVCs did not significantly reduce the rates of CRBSI for CVCs inserted in the subclavian vein, but did for trials using the femoral vein, jugular vein and a mixture of sites. One explanation for non-significant reduction in CRBSI for subclavian AI-CVCs is the low infection rates for the control (standard) CVCs (5%) compared with other sites (jugular 10% and femoral 11%), reducing the statistical power of these studies. Another possible explanation is that two out of the four studies looking exclusively at subclavian lines used externally treated CHSS CVCs that do not show a significant treatment effect regardless of site of insertion. In conclusion, AI-CVCs significantly reduce the risk of CRBSI in femoral, jugular and mixed site studies, but there is inconclusive evidence for AI-CVCs inserted into the subclavian vein.

Sensitivity analyses

In clinical practice patients may have more than one CVC inserted during their treatment. To reflect this some trials included more than one CVC in a single patient. Sensitivity analyses showed that, excluding studies that analysed by CVCs inserted rather than the number of patients, the conclusions for CRBSI, colonisation and local clinical signs only did not change from the overall results.

Blinding in clinical trials is important.[80] In these trials there are numerous stages where lack of blinding might have affected the care provided and the outcomes assessed (e.g. time of insertion, catheter care, extraction management). Sensitivity analysis did not indicate that a lack of blinding affected the results.

True randomisation of trials is essential in ensuring that all possible variables are comparable across arms. Sensitivity analyses, conducted for CRBSI and colonisation, showed that results for studies where true randomisation was not clearly reported were in line with the overall pooled results.

In summary, this review demonstrates that the use of AI-CVCs is clinically effective in reducing CRBSI rates compared with standard CVCs. This remains true even when sensitivity and subgroup analyses assessing the effect of confounding variables are conducted.

Chapter 5
Economic review

Full economic evaluations

Review of economic literature
The aim of this section is to summarise published cost-effectiveness analyses (CEAs) of AI-CVCs for the prevention of CRBSIs. The methods used for this review are described in the section 'Methods for reviewing cost-effectiveness' (p. 8).

Identification of studies
The economic reviewers scanned the titles and abstracts of the 182 articles identified by the electronic searches and handsearching, 35 of which were considered relevant. Finally, by searching the references of the papers obtained, a further seven articles were identified for possible inclusion in this review. These 42 articles were then assessed for inclusion in the review using the criteria previously described.

Quantity and quality of research available
Only four of the 42 papers assessed for inclusion in the review met the explicitly predefined criteria.[31,81–83] Three of these four studies reported the results of full economic evaluations; one study[81] was published as a letter. Overall, the quality of the full economic evaluation papers was high. However, the quality of the published letter was poor; owing to limited space, much of the information was provided in summary form or was only partially explained (for example, there was no discussion of discount rate or sensitivity analysis). Full details of the quality assessment exercise are presented in *Table 14*. None of the papers reported quantities of health resources separately from costs and only one study[82] included full details of price adjustments for inflation. From the data presented it was not possible to determine how Frank and colleagues[81] estimated the incremental cost-effectiveness ratios (ICERs) quoted. Also, in the paper by Shorr and colleagues[83] there is confusion regarding the base-case incidence rate of CRBSIs. In the text the number of CRBSIs identified is 31, and in the main results table it is shown as 33 CRBSIs, but the actual number used to calculate the ICERs is 34 CRBSIs.

In summary, all of the authors adequately described the research question and comprehensively described the relevant comparators. However, only Marciante[82] and Veenstra[31] provide the reader with enough information to recalculate and therefore verify the size of the ICERs.

Characteristics of economic evaluations
Three of the four studies were described as CEAs; the study conducted by Marciante[82] was a cost–utility analysis (CUA). In each of the studies, health outcomes were managed differently and a range of cost-effectiveness ratios was used: cost per infectious case, cost per quality-adjusted life-year (QALY) and cost per CRBSI avoided. As presented in *Table 15*, two of the studies[81,31] compared the use of CHSS CVCs with the use of standard CVCs; Marciante and colleagues[82] compared the use of CHSS CVCs versus MR CVCs; Shorr[83] compared standard CVCs versus CHSS or MR CVCs. In the Marciante[82] and Veenstra[31] studies, the CHSS and MR CVCs used were extraluminally coated; in the Shorr[83] study both the CHSS and MR CVCs were intraluminally and extraluminally coated. Although unstated, the date of publication suggests that the CHSS CVC used in the Frank[81] study is only coated on the external surface.

The study population in all of the papers was described as high risk or as admitted to a medical intensive care ward. The studies by Shorr[83] and Veenstra[31] used hypothetical cohorts of patients, while Frank[81] and Marciante[82] used efficacy data from patients who were participants in clinical trials. Marciante[82] looked at the costs and benefits of the new technologies over the lifetime of the patient, whereas the other papers appeared to focus on immediate costs and benefits. None of the economic evaluations included data from patients in the UK NHS.

Economic models
All of the studies include some form of economic model. Frank[81] estimated patient length of stay using statistical multistate models based on transitional probabilities. The remainder of the studies used decision-analytic models to incorporate benefits and costs. Each of the decision-analytic models relies on a different set of assumptions, as outlined in *Table 16*. In terms of outcomes, key assumptions relate to percentage of colonised CVCs associated with local infection,

TABLE 14 *Quality assessment exercise*

Checklist item	Frank[81]	Marciante[82]	Shorr[83]	Veenstra[31]
1. The research question is stated	✓	✓	✓	✓
2. The economic importance of the research question is stated	✓	✓	✓	✓
3. The viewpoint(s) of the analysis are clearly stated and justified	✓	✓	✓	✓
4. The rationale for choosing the alternative programmes or interventions compared is stated	X	✓	✓	✓
5. The alternatives being compared are clearly described	X	✓	✓	✓
6. The form of economic evaluation used is stated	✓	✓	✓	✓
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	✓	✓	✓
8. The source(s) of effectiveness estimates used are stated	✓	✓	✓	✓
9. Details of the design and results of effectiveness study are given (if based on a single study)	X	✓	✓	✓
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	X	NA	✓	✓
11. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	✓	✓	✓
12. Methods to value health states and other benefits are stated	X	✓	✓	✓
13. Details of the subjects from whom valuations were obtained are given	X	✓	NA	NA
14. Productivity changes (if included) are reported separately	NA	NA	NA	NA
15. The relevance of productivity changes to the study question is discussed if included	NA	NA	NA	NA
16. Quantities of resources are reported separately from their unit costs	X	X	X	X
17. Methods for the estimation of quantities and unit costs are described	X	P	P	✓
18. Currency and price data are recorded	✓	✓	✓	✓
19. Details of currency price adjustments for inflation or currency conversion are given	X	✓	P	P
20. Details of any model used are given	NA	✓	✓	✓
21. The choice of model used and the key parameters on which it is based are justified	NA	✓	✓	✓
22. The time-horizon of costs and benefits is stated	X	✓	X	✓
23. The discount rate(s) is stated	NA	NA	NA	NA
24. The choice of rate(s) is justified	NA	NA	NA	NA
25. An explanation is given if costs or benefits are not discounted	NA	NA	NA	NA
26. Details of statistical tests and confidence intervals are given for stochastic data	X	X	NA	NA
27. The approach to sensitivity analysis is given	X	✓	✓	✓
28. The choice of variables for sensitivity analysis is justified	X	✓	✓	✓
29. The ranges over which the variables are varied are stated	X	✓	✓	✓
30. Relevant alternatives are compared	X	✓	✓	✓
31. Incremental analysis is reported	✓	✓	✓	✓
32. Major outcomes are presented in a disaggregated as well as an aggregated form	P	X	P	✓
33. The answer to the study question is given	X	✓	✓	✓
34. Conclusions follow from the data reported	✓	✓	✓	✓
35. Conclusions are accompanied by the appropriate caveats	X	✓	✓	✓

✓, Fully addressed; X, not addressed; P, partially addressed.

TABLE 15 *Characteristics of economic studies*

Study	Type of evaluation and synthesis	Interventions	Study population	Country	Time-frame of study
Frank[81]	CEA; cost per infectious episode	CHSS-impregnated catheter vs conventional catheters	138 patients admitted to a medical ICU	Germany	NS
Marciante[82]	CUA; cost per QALY	MR catheters vs externally coated CHSS catheters (1–25 days)	Hospitalised adults at high risk of developing a CRBSI who were likely to require a triple-lumen, non-cuffed catheter for ⩾3 days. Average age = 56 years. As per trial	USA	Lifetime of the patient
Shorr[83]	CEA; cost per CRBSI averted	MR catheters or CHSS catheters vs uncoated CVCs	Critically ill patients requiring a CVC that was expected to be in place for >48 hours. Two hypothetical cohorts of 1000 patients each	USA	NS
Veenstra[31]	CEA; no synthesis performed owing to dominance	Short-term use (2–10 days) of CHSS-impregnated multilumen CVCs vs non-impregnated catheters	Hypothetical cohort of hospitalised patients at high risk for catheter-related infections (e.g. patients in ICUs, immunosuppressed patients and patients receiving TPN) requiring use of a CVC	USA	Period of hospitalisation (short-term use)

attributable mortality and hypersensitivity risk. In terms of costs, key assumptions relate to period of interest, CVC replacement strategy and expected additional hospital stay due to CRBSI.

Cost data and cost data sources

Three of the studies are US based and include currency (US dollars) and date information. The studies should be comparable in terms of costs as the price years are within a 4-year band (1998–2002). The remaining study[82] was conducted in Germany and the costs are expressed in euros. None of the authors presents quantities of resources separately from costs. Frank[81] describes the cost items included in the study in much detail, but fails to give individual cost estimates; the primary source of cost data used in this study appears to be from local sources. The remaining papers use a mix of previously published studies and local data sources to derive costs. As shown in *Table 17*, the additional costs of a CRBSI used in the studies are similar and range from $9738 to $10,920.

Health outcome data and data sources

None of the economic evaluations was carried out alongside an RCT, which means that none of the studies used cost and benefit data from the same source. However, randomised trial data were used to inform all of the studies. Shorr[83] uses original patient-level data from a large RCT, which compared CHSS CVCs with MR CVCs; Veenstra[31] and Marciante[82] both base their clinical effectiveness analysis on published trial data, including meta-analyses. Frank[81] uses data from a non-randomised clinical trial and meta-analysis of RCTs. As detailed in *Table 18*, the range of health outcomes used in the three full economic evaluations was similar and includes the incidence of CRBSI, incidence of local infection and attributable mortality. Marciante[82] and Veenstra[31] used similar estimates of attributable mortality (14% and 15%, respectively).

Cost-effectiveness ratios

The results of the CEAs are described in *Table 19*. Shorr,[83] Veenstra[31] and Frank[81] conclude that, for high-risk patients, the use of AI-CVCs compared with standard CVCs does lead to improved health outcomes and reduced costs. In addition, the results of the Marciante[82] study indicate that it is likely that the MR CVC is cost-effective compared with the externally coated CHSS CVC and suggest that this cost-effectiveness is likely to increase with the expected duration of catheterisation. Similarly,

TABLE 16 *Economic model*

Study	Type of model	Perspective	Model assumptions	
			Outcomes	**Costs and resource use**
Frank[81]	LOS estimated using statistical multistate models based on transitional probabilities	Large German university hospital	NS	NS
Marciante[82]	Series of decision models (n = 25) with patient-level clinical trial data	Healthcare payer	5% of colonised catheters (in the absence of a CRBSI) would be associated with signs of local infection Risk of death from CRBSI = 14% and is the same for both catheters Survival experience of high-risk patients is similar to that of patients hospitalised in an ICU Primary benefit of MR catheters is the reduced risk of local infection and CRBSI; any other complications (e.g. mechanical, hypersensitivity reactions or antimicrobial resistance) are equally likely for the two catheters No catheters could be replaced over a guidewire CHSS used as baseline technology	Costs limited to period of hospitalisation No costs or adverse events associated with catheter colonisation (without local infection) or catheter removal in the absence of CRBSI Protocol prohibited recatheterisation using a guidewire and so limited insertion of study catheters to new venepunctures Models do not take potential differences in risk of catheter or mechanical complications into account
Shorr[83]	Simple decision tree	Healthcare payer	Impact of CRBSI on mortality is not modelled as mortality is not viewed as a primary outcome in recent trials Potential for hypersensitivity reactions related to use of CHSS is not modelled	Cost of CRBSI: extra ICU LOS = 6 days; extra ward hospitalisation = 5 days; professional fees = $500; infected CVCs replaced by inexpensive traditional catheters. Total cost is significantly less than published figures
Veenstra[31]	Decision-analytic model using data from RCTs, meta-analyses and case–control studies	Healthcare payer	Some colonised catheters (without BSI) would be associated with signs of local infection (e.g. purulence or erythema) at the insertion site and therefore require replacement Hypersensitivity reaction was included as an adverse event CRBSI: standard 5.2% vs impregnated 3.0% Attributable mortality: 15%; hypersensitivity: 0.0111%; death from hypersensitivity: 7.7%	Model assumes that a locally infected catheter site without signs of BSI is managed by inserting a new catheter

TABLE 17 *Cost data and cost data sources*

Study	Cost items	Cost data sources	Additional cost of coated catheter	Additional cost of CRBSI	Currency, and currency year	Discount rate
Frank[81]	(a) Medications and blood products (b) Laboratory work, tests and examinations (c) Hospital administration costs including personnel costs	(a) Hospital pharmacy data (b) Hospital price list (c) Hospital administration database	Not clear	Not clear	Euros	NA
Marciante[82]	Additional cost of MR catheter; CRBSI; cost of managing a local infection	Previously published data	MR vs CHSS = $9.66	$10,920	2000 US dollars; inflated using consumer price index specific to medical care	NA
Shorr[83]	CHSS catheter, MR catheter, treatment of CRBSI, diagnosis of CRBSI: charge data	Charge data from billing department of hospital Previously published data	CHSS vs CVC = $25	$10,452	2002 US dollars	NA
Veenstra[31]	Additional cost of antiseptic catheter, CRBSI, hypersensitivity reaction, managing local infection (blood culture and replacing CVC)	*Per diem* local hospital costs, previously published data	CHSS vs CVC = $27 MR vs CVC = $38	$9,738	1998 US dollars	NA

Shorr[83] demonstrated that, of the two newer double-coated devices, MR CVCs perform better financially (per catheter placed and per CRBSI avoided) than CHSS CVCs.

The evaluations by Marciante[82] and Veenstra[31] do not include the calculation of ICERs because they recognise that the newer technologies are dominant (improved clinical effectiveness at lower cost) compared with the current standard CVCs. The calculation and meaning of the ICER used in the Frank[81] paper are unclear. In the Shorr[83] paper, the definitive size of the ICER is unknown and there appears to be an arithmetic error in the calculation (see explanation in the section 'Quantity and quality of research available', p. 61); however, it is clear that the AI-CVCs appear to be more cost-effective than the non-treated CVCs.

The three full economic evaluations all use multivariate sensitivity analysis (using Monte Carlo simulation) and confirm that even under extreme clinical and economic assumptions, AI-CVCs perform better than standard CVCs.

Summary of evidence and discussion

From the literature review presented above it appears that, from a health service perspective, the use of CVCs to prevent CRBSIs is a cost-effective option compared with the use of standard CVCs when used in high-risk populations. The conclusions of all of the papers in the review are in agreement that use of these novel technologies leads to better patient outcomes and reduced costs.

However, given that there are only four published papers included in the review, these findings should be treated with caution. In addition, as none of the papers in the review is set in the UK their relevance to the NHS may be somewhat limited.

To date, there are no head-to-head RCTs of the currently available CVCs. Marciante[82] used original trial data when comparing the use of CHSS and MR CVCs; however, these CVCs were externally coated and are no longer available for use in the USA, where the CEA was conducted.

TABLE 18 *Health outcome data and data sources*

Study	Efficacy data	Efficacy data sources	Health outcomes	Health outcome data sources	Attributable mortality	Discount rate
Frank[81]	NS	Meta-analysis	Catheter related infection (CRI); infectious episode; LOS with and without CRI	Meta-analysis	NS	NS
Marciante[82]	Risk of CRBSI was similar between groups for the first 10 days. After 10 days, the risk was higher in the CHSS arm. In summary, the MR catheters reduced the risk of CRBSI by 92%	Patient-level data from the original trial	(a) CRBSI, local infection given colonisation (b) Death due to CRBSI, life expectancy, utility (c) QALYs	(a) Original trial (b) Published literature (c) QALYs: life expectancy derived from a study of similar ICU patients. Utility values of lymphoma, leukaemia and congestive heart failure patients	14%	3%
Shorr[83]	Base case: assumed incidence of CRBSI was 3.3% with standard catheters and that CHSS and MR conferred an RRR for the development of CRBSI of 60% and 85%, respectively	Model estimates derived from prospective trials of CHSS and MR	(a) Baseline estimate of CRBSI (b) RR ratio for CRBSI (c) LOS	(a) Meta-analysis (b) Literature review (c) Published literature	Not modelled	NA
Veenstra[31]	Summary RR for CRBSI was 0.58; summary RR for catheter colonisation was 0.61	Meta-analysis of RCTs	(a) Incidence of CRBSI (b) Incidence of death attributable to CRBSI and/or hypersensitivity reaction (c) Incidence of local infection	(a) Meta-analysis (b) Previous published reports	15%	NA

CRI, catheter-related infection; RRR, relative risk reduction.

TABLE 19 *Cost-effectiveness results*

Study	Total costs	Total incremental costs	Total outcomes	Total incremental outcomes	Cost-effectiveness ratios	Sensitivity analysis	Conclusion	Industry author affiliation
Frank[81]	Patients with CRI: €10,199.64 Patients without CRI: €3,269.95	Additional costs per day and case: €82.50 Additional marginal cost per infectious episode = €231	Average infection rate: CHSS: 0–6.3% Standard: 0.3–7.5%	Not explicitly stated	Additional marginal costs per 1000 catheters for CHSS vs conventional catheters: €2,434.80	None stated	The use of antiseptic-impregnated catheters in the ICU appears to be cost-effective	NS
Marciante[82]	NS	8 days: $–67 15 days: $–260 22 days: $–294	NS	8 days: 0.009 QALYs; 15 days: 0.03 QALYs; 22 days: 0.034 QALYs	8 days: cost saving 15 days: cost saving 22 days: cost saving	Multivariate SA (Monte Carlo simulation); one-way SA and scenario analyses. Probability that MR catheters were cost-effective in patients catheterised for 8 and ⩾13 days was 91% and 97.4%. RR of CRBSI had a strong individual effect: MR catheters became cost-saving from 8–13 years. SAs demonstrated robustness of results	CVCs coated with MR are cost-effective for patients catheterised for ⩾1 week and lead to overall cost-savings when patients are catheterised for ⩾2 weeks or longer	NS
Shorr[83]	Standard CVC: $414.28 per patient; CHSS: $218.52 per patient; MR: $136.69 per patient	Standard vs CHSS: $195.76 Standard vs MR: $277.59 CHSS vs MR: $81.83	No. of CRBSI: standard CVC: 34; CHSS: 13.6; MR: 5.1	Standard vs CHSS: 20.4; standard vs MR: 28.9; CHSS vs MR: 8.5	Standard vs CHSS: $9596.47 per CRBSI avoided; standard vs MR: $9605.12 per CRBSI avoided; CHSS vs MR: $9625.88 per CRBSI avoided	Multivariate SA. With all inputs skewed by 50% against both the CHSS and the MR catheters, they remained economically attractive. Threshold values calculated for all variables. One-way SA also conducted Model is most sensitive to the cost of CRBSI, followed by CRBSI incidence and then RRR for CRBSI with MR	CHSS and MR catheters both save costs compared to the older, standard CVCs. MR catheters yield slightly more savings than CHSS catheters	NS

continued

TABLE 19 *Cost-effectiveness results (cont'd)*

Study	Total costs	Total incremental costs	Total outcomes	Total incremental outcomes	Cost-effectiveness ratios	Sensitivity analysis	Conclusion	Industry author affiliation
Veenstra[31]	Antiseptic-impregnated catheter: $336; standard catheter: $532	$–196	Antiseptic-impregnated catheter: 3% CRBSI; standard catheter: 5.2% Incidence of death due to CRBSI or hypersensitivity: 0.45% (antiseptic-impregnated CVC) vs 0.78% (standard catheter)	–2.2%	No ICERs were calculated because the intervention is dominant: greater efficacy and lower costs	Multivariate SA (Monte Carlo simulation); a series of one-way SAs. Worst case scenario SA	CHSS reduces the risk of CRBSIs and death and provides cost-savings compared to the use of standard catheters	Lead author supported by Roche

SA, sensitivity analysis.

Although externally coated CHSS CVCs are used in the UK, the second generation (double-coated) CHSS CVC is awaiting a CE marking and is not yet commercially available in the UK. Shorr[83] had to conduct indirect clinical comparisons to compare the newer double-coated CHSS and MR CVCs. Evidence from an RCT comparing these latest devices is required before definitive guidelines regarding choice of coated CVC can be drawn up.

None of the studies assumed a difference in the mechanical complications between the CHSS and the MR CVCs. However, anecdotal evidence[82] reports that the MR CVC might not be as user-friendly as the CHSS owing to potential mechanical complications such as stiff guidewires. No matter how cost-effective the MR CVC may be in theory, if it is difficult to use then it may not be well received by the medical community.

The results of the published cost-effectiveness studies included in the review are not generalisable to all hospitalised patients. The results of the four studies described in the review specifically relate to high-risk patients. The duration of catheterisation must also be taken into account when discussing cost-effectiveness. Marciante[82] demonstrated that cost-effectiveness increased in line with the duration of catheterisations. Shorr[83] did not address this point directly, but did state that study CVCs had to be in place for more than 48 hours. Veenstra[31] only explored the cost-effectiveness of short-term use of CVCs. Duration of catheterisation is an important consideration as the risk of a CRBSI is believed to increase the longer the CVC is *in situ*. Marciante[82] concludes that the use of AI-CVCs in high-risk patients should reflect the expected duration of catheterisation. Further research is required to estimate the cost-effectiveness of AI-CVCs for different subgroups of patients.

CEA depends on two distinct elements (benefits and costs) and it is important that the size of the clinical benefit associated with these new CVCs is accurately measured. The authors of the economic evaluations explicitly state that the clinical efficacy demonstrated in the RCTs may not translate into clinical effectiveness. In the RCTs conducted, those involved in the insertion and maintenance of CVCs would have been trained in the use of optimal aseptic techniques and, owing to routine monitoring, strict adherence to study protocol would have ensured that stringent infection control policies were followed. Whether or not the same high standards can be expected in non-trial situations is subject to debate and therefore the size of the reduction in CRBSI in day-to-day clinical practice may differ from that experienced in the RCTs. It is also possible that the majority of hospitals involved in the RCTs were large teaching hospitals with higher than average CRBSI rates; smaller hospitals may not have the potential to reduce their CRBSI rates by the same differential.

A recurring theme discussed in the review papers is the reliance on previously published clinical and economic data; this is seen as a study limitation as the quality of studies can vary greatly. Veenstra[31] estimates that a "randomized trial with 90% power to detect a statistically significant difference in mortality would require more than 10,000 patients in each study arm", and it is therefore unlikely that such a trial would ever take place. Decision-analytic modelling is therefore a valid option for the assessment of the costs and benefits of preventing CRBSIs, but in order to improve the transparency of complicated models, quality assessment should be undertaken.

The costs of preventing CRBSIs using AI-CVCs must also be scrutinised. In practice, the costs of treating a CRBSI episode may vary substantially between healthcare providers and also between patients. In the reported sensitivity analyses, the results of the studies were robust when the cost of a CRBSI was varied within a reasonable range; however, in the Veenstra[31] and Shorr[83] studies the results were most sensitive to the cost of the CRBSI. The size of the potential savings from the prevention of CRBSIs is in part determined by the cost of treating a CRBSI; overestimates of the cost of the CRBSI will lead to an overestimate of the benefits of preventing CRBSIs.

Further research into the likelihood of hypersensitivity reactions and/or a build-up of antibacterial resistance must also be investigated to ensure that potentially serious complications do not offset the benefits of CHSS and MR CVCs.

In summary, the current published evidence suggests that AI-CVCs are cost-effective compared with standard CVCs for high-risk patients. However, given the paucity of the economic evidence available, the results of these studies must be interpreted carefully.

Economic evidence: partial economic evaluations

As the review of the economic literature shows, there are few published full CEAs comparing different types of CVCs for the prevention of

CRBSIs. However, there are many published economic studies which include estimates of cost-savings associated with the prevention of BSIs and CRBSIs. *Table 20* summarises a range of papers that include estimates of possible monetary savings associated with the prevention of CRBSIs. All of these papers have been identified from the original search of electronic databases as described in the section 'Methods for reviewing cost-effectiveness' (p. 8). This group of papers did not meet the entry criteria for inclusion in the review as they are partial, not full, economic analyses.

Study characteristics

Of the 16 studies, 14 are from authors in the USA; the remaining two are from Spain and Argentina. The studies were published during the period 1995–2004. The majority of studies were restricted to patients from surgical or medical intensive care wards, the remainder featuring a mix of hospital departments.

Nine of the 16 papers compared different types of CVCs: CHSS versus standard CVCs ($n = 3$), MR versus standard CVCs ($n = 2$), and CHSS and/or MR versus standard CVCs ($n = 4$). Of the remainder, three focused on other options (improved vascular site care, adoption of a multifaceted systems approach and stringent use of MSBs). Another three papers estimated the additional resources consumed by patients with CRBSIs compared with those patients who did not have a CRBSI; two of these papers used matched controls. Finally, one editorial summarised the evolving technology of vascular access and included an estimate of potential savings.

Rate of CRBSI

Rates of CRBSI used in the studies vary. This is appropriate as the studies focus on different patient groups. It is likely that high-risk groups will have higher rates of CRBSI. Also, different hospitals have different infection control policies and therefore may employ different definitions of CRBSI. CRBSI rates are also expressed differently, including: rate per 1000 catheter days, rate per 1000 patient days, percentages and rate per 100 admissions to an ICU. All of the studies show that the rate of CRBSI can be reduced by the introduction of novel technologies. Some studies discuss rates of BSI only.

Extra cost of a CRBSI

In the studies, the additional costs of a CRBSI range from $812 to $71,000. In the only European study, the extra cost of a CRI is €3124. When estimating the extra cost of a CRBSI, the main cost driver is the number of additional days spent in hospital. Whether or not a patient's stay is extended in a general ward and/or in an intensive care ward also affects the size of the cost estimate. Dimick[84] reports that CRBSIs can extend a patient's hospital stay by 20 days in an intensive care ward or by 22 days in a general medical ward; the extra cost of a CRBSI of $71,443, as reported by Dimick,[84] is the highest cost of all the studies presented.

When estimating the extra cost of a CRBSI, four of the 16 studies[40,85,86,87] refer to the paper by Pittet and colleagues.[88] This paper reports a pairwise-matched case–control study designed to determine the excess length of stay, extra costs and mortality attributable to nosocomial BSI in critically ill patients. The extra hospital and intensive care lengths of stay attributable to BSI were 24 and 8 days, respectively. Pittet[88] estimated that the average additional cost of a BSI was $40,000 per survivor. This figure is not specifically associated with CRBSIs; however, it is likely that the cost difference between a BSI and a CRBSI is minimal.

Attributable mortality

In the studies presented, the rates reported in or quoted by the studies vary from 0% to 35%. Again, the rate of attributable mortality is expected to vary depending on the health status of the patient and the infection control policy of the host institution. Definitions of 'attributable' must be stated carefully. For example, if following cardiac surgery a patient recovers from a CRBSI but dies at a later date owing to the stress imposed by multiorgan dysfunction, is this death attributable to the CRBSI? Clearly, when comparing mortality rates, it is important to ensure that similar groups of patients are being compared and that definitions of the patient populations are explicitly stated.

In summary, as RCTs in this area do not include mortality as a primary outcome measure, there exists considerable controversy about the size of attributable mortality. Recent studies suggest that if adjustments are made for the patient's health state before infection, then the attributable mortality risk may be smaller than is currently assumed.[89] In any good quality economic evaluation the reference case rate will be varied within the sensitivity analysis.

Potential savings from preventing CRBSIs

All but one of the studies presented in *Table 20* explicitly agrees that there are substantial

TABLE 20 *CRBSI: summary of rates and costs*

Study	Year	Country	Objective	Setting	Study assumptions			Authors' conclusions
					CRBSI rate	Extra cost of CRBSI	Attributable mortality	
Booth,[90] as reported by Booth[90] and Civetta[27]	1995	USA	To compare outcomes and cost-effectiveness between antiseptic-impregnated (CHSS) and standard CVCs	Surgery	Significant pathogen identified: Standard CVCs: 25/54 (46%); impregnated CVCs: 8/42 (19%)	Not explicitly stated	Not explicitly stated	Anticipated annualised hospital charge savings through full conversion to CVCs with CHSS were estimated to be $8005/standard catheter replaced/patient or a total net saving in excess of $8 million
Berenholtz[91]	2004	USA	To determine whether a multifaceted systems intervention would eliminate CRBSIs	ICU	Study ICU at baseline: 11.3/1000 catheter days; postintervention: 0/1000 catheter days Control ICU at baseline: 5.7/1000 catheter days; postintervention: 1.6/1000 catheter days	$45,254 ($34,508–56,000)	18% (0–35%)	Authors estimated that in their surgical unit alone they may have prevented up to 43 CRBSIs and eight deaths, and saved nearly $2 million in additional costs per year
Chaiyakunapruk[92]	2003	USA	To evaluate the cost-effectiveness of CG compared with PI for vascular catheter site care	Hospital	PI: 3.08% (1.9–4.26%); CG: 0.49% (0.28–0.88%)	$7113 ($812–12,395) (2001 $)	15% (4.4–25%)	CG instead of PI is a simple and cost-effective method of improving patient safety in the hospital
Civetta[27]	1996	USA	To provide guidelines for the reduction of infection risks and costs using antiseptic-impregnated non-tunnelled CVCs	Hospital	Hypothetical example: Standard CVC: 2%; CVC + SSC: 1%	$6000 ($6000–32,000)	Up to 10–20% in high-risk populations	Estimated annual net cost-saving to the hospital is $35,000 (based on 1000 catheters per year)

continued

TABLE 20 *CRBSI: summary of rates and costs (cont'd)*

Study	Year	Country	Objective	Setting	Study assumptions			Authors' conclusions
					CRBSI rate	**Extra cost of CRBSI**	**Attributable mortality**	
Dimick[84]	2001	USA	To estimate the increased resource use associated with CRBSI specifically for critically ill surgical patients	Surgical ICU	Incidence of CRBSI per 1000 catheter days: 3.6 episodes (2.1–5.8)	$56,167 (total hospital cost); $71,443 (ICU cost) (1998 $)	Hospital: 35%; ICU: 33%	Study demonstrates a profound increase in healthcare costs and LOS associated with CRBSI in critically ill surgical patients
Hanna[85]	2003	USA	To evaluate the impact of using CVCs impregnated with MR on nosocomial bloodstream infections, morbidity and mortality in cancer patients	Cancer patients in ICU	Baseline: 3.1/1000 patient days; postintervention: 0.7/1000 patient days	$44,864 (1998 $)	BSI mortality: Medical unit: before: 0.3%, after 0% Surgical unit: before 1.2%, after 0.6%	The introduction of AICs to the adult medical and surgical units was associated with a significant decrease in nosocomial BSIs. This significant decrease resulted in net savings of at least $1,450,000 during 1999
Hu[86]	2004	USA	To estimate the clinical and economic consequences of using MSBs, compared with less stringent sterile barrier techniques when placing a CVC	ICU	Stringent MSB: 2.8%; less stringent (MSB): 5.3%	$9738 ($6005–28,690) ($11,469, 2003 $)	15% (4–25%)	Authors conclude that for every 270 catheters placed with the use of MSBs, approximately $70,000 would be saved, and seven episodes of CRBSI and one death would be avoided
Maki[58]	1997	USA	To determine the efficacy of standard CVC vs CVC+SSC	Medical/surgical ICU	CVC: 7.6 infections/ 1000 catheter days; CVC+SSC: 1.6 infections/1000 days	$29,000 (1995 $)	10–25%	If the antiseptic catheter reduces the risk of CRBSI by at least 50%, the use of such catheters should prove to be cost-beneficial

continued

TABLE 20 *CRBSI: summary of rates and costs (cont'd)*

Study	Year	Country	Objective	Setting	Study assumptions			Authors' conclusions
					CRBSI rate	Extra cost of CRBSI	Attributable mortality	
Marin[4]	2000	USA	To review the prevention of nosocomial bloodstream infections: effectiveness of antimicrobial-impregnated and heparin-bonded CVCs	Range of departments	Standard CVC: 5.1%; CVC + anti-infective: 2.78%	NS	NS	If the cost of treating a CRBSI is greater than $3495, then the anti-infective catheters can be considered to be cost-effective
Oinonen[87]	2000	USA	To undertake a qualitative review of the literature on antimicrobial CVCs and economic assessment	Range of departments	CHSS catheter group: 3.2%; MR catheter group: 1.2%; standard CVC: 5.2%	$25,000	NA	Savings from using CHSS catheters appear favourable. Researchers estimated that the use of MR catheters could save the average academic medical centre (using at least 850 catheters) more than $500,000 per year
Pai[6]	2001	USA	To perform a critical review of the literature to provide clinicians with a summary of the data supporting the use of catheters for the prevention of catheter-colonisation and CRBIs	Range of departments	Incidence of CRBSI = 4%; reduction in CRBSI with MR: 3–5%; reduction in CRBSI with CHSS: 1–2%	$6000–10,000	14–24%	Assuming a marginal cost of $40 per catheter, cost–savings could reach $100 million
Raad[38]	1997	USA	To determine the efficacy of catheters coated with MR in preventing catheter-related colonisation and bloodstream infections	Hospital	Uncoated catheters: 5%; coated catheters: 0%	$14,345–100,415	No mortality associated with CRBSI	If annual number of inserted catheters = 850, catheters coated with MR hospital savings could reach $500,00 per year

continued

TABLE 20 *CRBSI: summary of rates and costs (cont'd)*

Study	Year	Country	Objective	Setting	Study assumptions			Authors' conclusions
					CRBSI rate	**Extra cost of CRBSI**	**Attributable mortality**	
Rello[89]	2000	Spain	To determine the consequences of CRI acquired in ICUs in terms of attributable mortality, increased LOS and excess costs (matched control)	ICU	Incidence of CRI: 2.85 episodes/100 admissions to ICU	€3124 per survivor of a CRI	No significant differences in overall mortality (23.7% vs 24.3%). No difference in attributable mortality identified	CRIs lead to increased hospital stay and increased costs
Rosenthal[93]	2003	Argentina	To determine the attributable excess costs with CVC associated BSIs in patients from cardiac and medical/surgical ICUs (matched analysis)	ICU	CVC-associated BSI: 2.92% of patients	$2975 (Argentinian $, 2002)	24.6%	Patients with CVC-associated BSI experienced significant prolongation of hospitalisation, increased use of healthcare resources and a higher attributable mortality
Saint[40]	2000	USA	To estimate the clinical and economic consequences of nosocomial CVC-related infections	Range of departments	Non-coated catheters: 5.2% (3.9–6.5%); decrease in incidence of CRBSI with coated catheters: OR 0.56	$6005–9738	4–20%	In light of the substantial clinical and economic burden of CRI, hospital personnel should adopt proven cost-effective methods to reduce this common and important nosocomial complication

continued

TABLE 20 *CRBSI: summary of rates and costs (cont'd)*

Study	Year	Country	Objective	Setting	Study assumptions			Authors' conclusions
					CRBSI rate	**Extra cost of CRBSI**	**Attributable mortality**	
Wenzel[94]	1999	USA	To discuss the evolving technology of venous access	Hospital	Coated catheters prevent 32 infections/ 1000 patients and 8 attributable deaths/ 1000 patients	CHSS: extra cost of preventing an infection: $1563; extra cost of preventing a death: $6250 MR: extra cost of preventing an infection: $3125; extra cost of preventing a death: $12,500	BSI: 25%; CRBSI: 8/1000 patients	There exists the potential for reducing morbidity and mortality at reasonable costs. The authors favour expanded use of effective second generation catheters in critical care units

AIC, anti-infective catheter.

monetary savings to be generated from successfully reducing the number of bloodstream infections. Anticipated savings are related to the number of CVCs inserted in specific patient groups per year. Only the results of the Spanish study appear to be somewhat cautious; Rello and colleagues[89] conclude that catheter-related infections lead to increased costs and that the potential economic benefits of new techniques to prevent intravascular catheter-related infections need to be explored.

Economic evaluation for the NHS in England and Wales

None of the published full or partial economic analyses described in the preceding sections is directly relevant to the UK NHS. The aim of this section of the report is therefore to estimate the economic performance (cost-effectiveness and potential cost-savings) of using AI-CVCs to reduce the number of CRBSIs in patients requiring a CVC for the NHS in England and Wales.

Current NHS use of CVCs

There is no up-to-date estimate of the number of CVCs inserted annually in the NHS in England and Wales. The difficulties of deriving such estimates are outlined in a recent HTA report by Calvert and colleagues.[95] In an attempt to obtain a reliable estimate of the number of CVCs placed annually, the present authors contacted NHS Logistics, which supplies NHS trusts and primary care trusts with a wide range of CVCs. NHS Logistics estimated that they supplied approximately 238,500 CVCs to the NHS in England and Wales between March 2004 and April 2005. Whether or not all 238,500 CVCs were used is unknown. Ten suppliers of CVCs in the UK were also surveyed. Responses were received from five, three of which (Arrow, Edwards Life Sciences and B. Braun) were willing to share information with the researchers. However, it was not possible to ascertain whether these CVCs were supplied to NHS trusts and/or to private hospitals in England and Wales.

Simple economic model

A basic decision-analytic model was constructed to explore a range of possible scenarios for the NHS in England and Wales. For simplicity, the comparison in the model is between any standard CVCs and any AI-CVCs. Therefore, the model does not differentiate between, for example, MR CVCs or CHSS CVCs; as a result, this excludes the cost of treating hypersensitivity or of any deaths from hypersensitivity which may occur when using a CHSS CVC. The authors have chosen not to include a measure of the costs or benefits of local infection. Finally, the authors have elected not to model the potential number of deaths avoided as a direct benefit of using AI-CVCs, following Shorr's[83] example, as the rates of attributable mortality vary greatly in the literature. For example, Veenstra and colleagues,[31] in their sensitivity analysis, state a range of attributable mortality between 0% and 35%.

The simple decision tree in *Figure 27* describes the possible alternative choices, uncertain events and outcomes for patients requiring a CVC.

Table 21 shows the variable parameters in the decision tree, the baseline values used in the model and a possible range of values for each parameter. Given that there is a paucity of UK NHS data in this area, there is much uncertainty surrounding parameter estimates; sensitivity analysis using values from the ranges shown was therefore undertaken.

Baseline assumptions

Outcomes

It is estimated that approximately 3%[23] of patients will experience a CRBSI as a result of having a standard CVC inserted. The results of the meta-analysis (see the section 'All studies', p. 39) comparing standard CVCs with (any) AI-CVCs demonstrate that using AI-CVCs can lead to a 54% reduction in the number of CRBSIs experienced by patients (RR 0.46, 95% CI 0.34 to 0.62). This

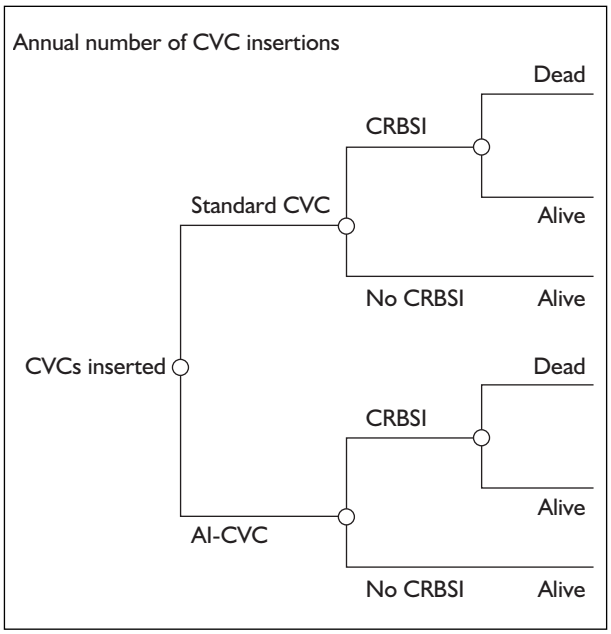

FIGURE 27 *Simple decision tree*

TABLE 21 *Model parameters and estimated values*

Model parameter	Value	Source	Range	Source
Incidence of CRBSI with CVC	3%	Fletcher[23]	2%[27] to 5%[4]	Published literature
RRR in CRBSI with AI-CVCs compared with CVCs	54%	LRiG meta-analysis[b]	38% to 66%	LRiG meta-analysis (upper and lower confidence interval of RRR[b])
Cost of CRBSI	£9148[a]	Estimate based on published economic evaluations[83,31]	£2500[89] to £71,000[84]	Published literature
Price differential between CVC and AI-CVC	£10	Estimate from analysis of NHS Logistics Catalogue[96]	£2.50[96] to £25[83]	Published literature

[a] Cost per day in ICU and general medical ward taken from Walker *et al*. (2006).[97]
[b] See *Figure 2* on page 39.
LRiG, Liverpool Reviews and Implementation Group.

means that the number of patients experiencing a CRBSI in a population of 238,500 would fall from 7155 (3%) to 3291 (1.38%) if all patients were treated with AI-CVCs instead of standard CVCs.

The base-case scenario did not include an estimate of attributable mortality. This assumption renders the model conservative and favours the use of standard CVCs as the potential benefits of reduced deaths from CRBSI with AI-CVCs are not explicitly recognised.

Costs

The cost of treating a CRBSI is the same whether or not a CVC or an AI-CVC is confirmed as the cause of infection. The true cost of a CRBSI is driven by the patient's length of stay in ICU and/or in a general medical ward. Currently there are no published estimates of patient length of stay due to a CRBSI for patients in England and Wales. In line with the more recently published economic evaluations,[31,83] it was assumed that a patient with a CRBSI spends 6 additional days in ICU and 5 additional days in a general medical ward.

Based on information from suppliers, it was assumed that there is a price differential of approximately £10 between AI-CVCs and CVCs. Analysis of NHS Logistics catalogue prices (2005/06) suggests that this price premium may be as low as £2.50.

Results: baseline incremental cost per patient

An incremental cost per patient with an AI-CVC instead of a standard CVC was calculated as follows:

$$\text{Incremental cost per patient} = E - (\text{CRBSI} \times \text{InCVC} \times \text{RRR})$$

where E = extra cost per AI-CVC inserted (£10), CRBSI = additional treatment cost per CRBSI episode (£9148), InCVC = incidence rate of CRBSI with standard CVC (0.03), and RRR = relative risk reduction in CRBSI when AI-CVC replaces standard CVC (0.54).

The incremental cost per patient was estimated to be equal to –£138.20; that is, for every patient who receives an AI-CVC, there is an estimated cost-saving of £138.20.

Results: multivariate sensitivity analysis

To determine the robustness of the estimated incremental cost per patient, a multivariate sensitivity analysis was performed. Using the minimum and maximum values of the key parameters as listed in *Table 21*, estimates are provided of the possible range of incremental costs per patient (*Table 22*). It is clear that under a wide range of clinical and cost assumptions, the use of AI-CVCs leads to negative incremental costs per patient; that is, cost-savings. Potential incremental cost-savings range from £2 to £2318 per patient.

Only one out of 81 scenarios presented does not show a cost-saving. As expected, the least incremental cost-savings identified occur with the most extreme negative assumptions associated with AI-CVCs (highest cost differential, lowest health benefit, least expensive CRBSI costs and lowest incidence of CRBSI with a standard CVC).

TABLE 22 *Multivariate sensitivity analysis of incremental cost per patient*

		Cost of CRBSI								
		£2500	£2500	£2500	£9148	£9148	£9148	£71,000	£71,000	£71,000
Extra cost of AI-CVC	**RRR with AI-CVC**	**Incidence of CRBSI with CVC (%)**								
		2.0	**3.0**	**5.0**	**2.0**	**3.0**	**5.0**	**2.0**	**3.0**	**5.0**
£2.50	0.38	–£17	–£26	–£45	–£67	–£102	–£171	–£537	–£807	–£1,347
£2.50	0.54	–£25	–£38	–£65	–£96	–£146	–£244	–£764	–£1,148	–£1,915
£2.50	0.66	–£31	–£47	–£80	–£118	–£179	–£299	–£935	–£1,403	—£2,341
£10.00	0.38	–£9	–£19	–£38	–£60	–£94	–£164	–£530	–£799	–£1,339
£10.00	0.54	–£17	–£31	–£58	–£89	–£138	–£237	–£757	–£1,140	–£1,907
£10.00	0.66	–£23	–£40	–£73	–£111	–£171	–£292	–£927	–£1,396	–£2,333
£25.00	0.38	**£6**	–£4	–£23	–£45	–£79	–£149	–£515	–£784	–£1,324
£25.00	0.54	–£2	–£16	–£43	–£74	–£123	–£222	–£742	–£1,125	–£1,892
£25.00	0.66	–£8	–£25	–£58	–£96	–£156	–£277	–£912	–£1,381	–£2,318

It is very unlikely that these assumptions would be valid simultaneously in the real world.

Results: breakeven parameter values

It is also possible to estimate the breakeven values for each of the key parameters, which would make a decision-maker indifferent to a choice between AI-CVCs and standard CVCs based on costs alone, as neither savings nor losses are incurred.

This involves setting the expression for incremental cost equal to zero, and solving for the value of the selected parameter, while other variables assume their central values:

- the price differential would need to rise to £148.20 (from £10), or
- the relative risk reduction would need to fall to 0.036 (from 0.54), or
- the cost of a CRBSI would need to fall to £617.28 (from £9148), or
- the incidence of CRBSI with standard CVC would need to fall to 0.2% (from 3%).

None of the clinical or cost evidence so far identified in this review supports the use of any of these parameter values. Therefore, on the basis of these simple calculations, it appears that given a choice, AI-CVCs are to be preferred over standard CVCs from a health economics perspective. In cost-effectiveness terms, AI-CVCs dominate standard CVCs as they are cheaper and more effective.

Results: incremental CRBSIs avoided with AI-CVCs

It is useful to estimate the number of incremental CRBSIs avoided when AI-CVCs are used instead of standard CVCs. *Table 23* shows the number of CRBSIs prevented per 1000 patients treated under different assumptions of the incidence of CRBSI with standard CVCs and a reduced risk of CRBSI with AI-CVCs.

TABLE 23 *Number of CRBSIs prevented per 1000 patients treated*

	Incidence of CRBSI with CVC (%)		
RRR with AI-CVC	**2.0**	**3.0**	**5.0**
0.38	7.6	11.4	19.0
0.54	10.8	16.2	27.0
0.66	13.2	19.8	33.0

If one estimates that the number of CVCs used in the NHS in England and Wales per annum is 238,500, the number of CRBSIs avoided by using AI-CVCs instead of standard CVCs ranges from 1812 (CVC infection rate = 2%, RRR = 0.38%) to 7870 (CVC infection rate = 5%, RRR = 0.66%), depending on the assumptions used.

Results: cost per CRBSI avoided

Having calculated an incremental cost per patient and estimated the number of incremental CRBSIs prevented per patient, we can take the final step of calculating ICERs. As shown in *Table 24*, the use of AI-CVCs dominates the use of standard CVCs as AI-CVCs are more effective and cost less.

Discussion of economic model

The results of the simple decision-analytic model presented here show that the use of AI-CVCs instead of standard CVCs can lead to a reduction in CRBSIs and decreased medical costs. The

TABLE 24 *Incremental cost per CRBSI prevented*

		Cost of CRBSI								
		£2500	£2500	£2500	£9148	£9148	£9148	£71,000	£71,000	£71,000
Extra cost of AI-CVC	**RRR with AI-CVC**	**Incidence of CRBSI with CVC (%)**								
		2.0	**3.0**	**5.0**	**2.0**	**3.0**	**5.0**	**2.0**	**3.0**	**5.0**
£2.50	0.38	–£2171	–£2281	–£2368	–£8819	–£8929	–£9016	–£70,671	–£70,781	–£70,868
£2.50	0.54	–£2269	–£2346	–£2407	–£8917	–£8994	–£9055	–£70,769	–£70,846	–£70,907
£2.50	0.66	–£2311	–£2374	–£2424	–£8959	–£9022	–£9072	–£70,811	–£70,874	–£70,924
£10.00	0.38	–£1184	–£1623	–£1974	–£7832	–£8271	–£8622	–£69,684	–£70,123	–£70,474
£10.00	0.54	–£1574	–£1883	–£2130	–£8222	–£8531	–£8778	–£70,074	–£70,383	–£70,630
£10.00	0.66	–£1742	–£1995	–£2197	–£8390	–£8643	–£8845	–£70,242	–£70,495	–£70,697
£25.00	0.38	**£789**	–£307	–£1184	–£5859	–£6955	–£7832	–£67,711	–£68,807	–£69,684
£25.00	0.54	–£185	–£957	–£1574	–£6833	–£7605	–£8222	–£68,685	–£69,457	–£70,074
£25.00	0.66	–£606	–£1237	–£1742	–£7254	–£7885	–£8390	–£69,106	–£69,737	–£70,242

results of a series of multivariate sensitivity analyses reveal that estimates of potentially large cost-savings, depending on the size of the population, may be anticipated under a wide range of cost and clinical assumptions.

Clearly, the size of any cost-savings is driven by a number of factors, including number of CVCs inserted, aseptic insertion technique, size of the reduction in CRBSIs due to use of AI-CVCs, health status of the patient, treatment of CRBSI and the size of the price premium between different types of CVCs. For a full economic evaluation to be performed, relevant England and Wales NHS data describing each of these factors would be required. As this information is not currently available, ICERs were estimated for a range of different assumptions and it was demonstrated that all reasonable scenarios show AI-CVCs to be dominant, as they are cheaper and lead to a reduced number of CRBSIs for patients. A comprehensive CEA of the options would also include the costs and health outcomes associated with hypersensitivity, the costs and benefits of local infections, assumptions about attributable mortality and specification of CVC type.

Decision-makers in the NHS should interpret the results of these analyses with caution, ensuring that their patient populations and the important characteristics of local clinical practice are indeed similar to those described in these calculations. In particular, it should be noted that the size of the benefit assumed from AI-CVCs compared with standard CVCs is the result of a meta-analysis which included a mix of high-risk (ICU, surgery, cancer) and low-risk (hospital) patients. In addition, the analyses compare standard CVCs with the available AI-CVCs as a class, and do not differentiate between types of AI-CVC.

Chapter 6

Discussion and conclusions

Discussion

This review assessed the clinical effectiveness of the use of AI-CVCs. Overall, the results of the review suggest that the use of AI-CVCs is clinically effective and cost-effective compared with standard CVCs.

Four trials compared treated catheters with each other. One of these reported a benefit of antibiotic-treated catheters over catheters treated externally with CHSS. Further research is required before any recommendation related to the effectiveness of specific treated catheter types can be made.

In contrast to the results of this review, previous reviews demonstrated that the externally treated CHSS catheters were clinically effective at reducing CRBSI rates (see Appendix 1). In particular, Veenstra and colleagues,[2] who only assessed the clinical effectiveness of externally treated CHSS CVCs, showed that these AI-CVCs significantly reduced CRBSIs compared with standard CVCs. There may be a number of reasons to explain why the present findings differ from those of Veenstra and colleagues.[2]

The table in Appendix 1 lists the studies included in previous and current reviews of AI-CVCs compared with standard CVCs. As can be seen, the present review excludes a number of poor-quality studies; for example, those without true randomisation, those presenting only interim data, where limited data was available in abstract form only, or those that included non-standard catheter designs such as dipped/bathed catheters. All but one[2] previous review included a mix of catheter types in the analysis; Veenstra[2] included only externally treated CHSS catheters and reported a reduction in both CRBSI and colonisation rates. In the Veenstra review,[2] the meta-analysis included interim results from two studies,[98,99] as well as data from two studies that did report true randomisation (e.g. used patient record numbers to randomise).[50,51] In addition, the review by Veenstra[2] did not include the results of a large study[57] published 2 years previously that failed to demonstrate clinical superiority of externally treated CHSS CVCs compared with standard CVCs. Veenstra and colleagues[2] argued that the technique of withdrawing blood through the CVC for microbiological analysis in the Logghe[57] trial did not meet their inclusion criteria for diagnosis of CRBSI. Owing to the outcome categorisation system used in the current review, the method used by Logghe[57] met the present inclusion criteria for diagnosis of CRBSI. Exclusion of poor-quality studies and inclusion of the study by Logghe[57] is likely to explain why the findings of Veenstra[2] differ from those presented in this review that indicate that externally treated CHSS CVCs are not clinically effective compared with standard CVCs.

This review supports the conclusions of previous reviews which highlighted the poor methodological quality of research in this area; more recent studies still fail to demonstrate improvements in reporting (e.g. failure to truly randomise, inadequate blinding). In light of this, McConnell and colleagues[5] recently argued that the case for the clinical effectiveness of anti-infective catheters had not been proven and lobbied for a large trial that would be powered to assess the impact of AI-CVCs on CRBSI rates. It appears that their proposed trial did not secure funding and therefore such a trial has not been conducted.

In this study, a review of the cost-effectiveness of AI-CVCs compared with standard CVCs was also conducted. The findings of the four included studies, none of which is UK based, demonstrate that AI-CVCs are cost-effective for high-risk patients. However, given the paucity of the economic evidence available, the results of these studies must be interpreted carefully. The results of the simple decision-analytic model demonstrate that the use of AI-CVCs (as a class) instead of standard CVCs in the NHS can lead to a reduction in CRBSIs and decreased medical costs. The results of a series of multivariate sensitivity analyses on the economic data reveal that potentially large cost-savings, depending on the size of the population, may be anticipated under a wide range of cost and clinical assumptions.

It was not possible to conduct a full economic evaluation as there is limited and/or poor-quality data available on a number of key aspects (i.e. the number of CVCs inserted in the UK NHS, typical aseptic insertion techniques used, size of the reduction in CRBSIs due to use of AI-CVCs, patient health status, treatment pathways for CRBSI and the size of the price premium between different types of CVCs). Decision-makers must ensure that their patient populations and the important characteristics of local clinical practice are indeed similar to those described in these calculations before any changes to clinical practice are made.

It was not the remit of this report to consider the multifactorial issues around prevention of CRBSIs. The existence of multifactorial issues is highlighted by the fact that the use of AI-CVCs by no means guarantees protection against CRBSI. Individual studies still report significant CRBSI rates despite their use, even in research settings.

Data from a variety of clinical studies confirm that rates of CRBSI are variable. In the 32 included trials CRBSI rates ranged between less than 1%[18] and 16%[66] for standard CVCs, and between 0%[9,15,18,38,53] and 6%[69] for AI-CVCs. In two trials[9,18] the control arms reported CRBSI rates of 0.83% and 0.95%, confirming that low rates of infection are possible without recourse to the use of AI-CVCs. These variable infection rates, viewed from the perspective of the number needed to treat, mean that the number of patients who would need to receive a treated catheter to prevent one CRBSI could range from as low as 13 to as high as 221.

Such variations provide support for the argument that a more comprehensive approach to the problem of CRBSI is required. That is, effective and sustained prevention of CRBSIs demands a bundle of healthcare interventions at clinical and organisational levels. Essentially, these fall into two broad categories, namely asepsis and antisepsis (the use of antimicrobials). Asepsis, including attention to the use of aseptic technique at the time of catheter insertion and during catheter care, has been shown to be effective in preventing CRBSIs. This underpins all healthcare activity, not just invasive procedures. Antisepsis includes a range of antiseptic technologies such as AI-CVCs and Biopatch. Current recommendations for good practice are outlined in the EPIC guidelines.[25]

It has been highlighted in this report that several factors influence the clinical effectiveness and cost-effectiveness of AI-CVCs to reduce CRBSI rates compared with standard CVCs; these include study design factors, diagnosis of CRBSI, patient population and practice characteristics. In addition, relevant NHS information on resource-use and cost data is required before reliable estimates of cost-effectiveness can be generated.

Conclusions

The use of AI-CVCs reduces the rates of CRBSI for durations of between 5 and 12 days and greater than 20 days when CVCs are inserted in the femoral or jugular veins. Studies report the best clinical effect when CVCs are treated with MR or internally and externally treated with silver or CHSS. Further evidence is needed to confirm or refute the benefits of externally treated catheters, most notably the catheters treated with CHSS.

There is limited research evidence comparing treated catheters. Further research is required before any recommendation related to the effectiveness of specific types of treated catheters can be made.

Further evidence is required to test whether AI-CVCs reduce CRBSI for durations of between 13 and 20 days and for CVCs inserted into the subclavian vein.

Current published evidence suggests that AI-CVCs are cost-effective for high-risk patients compared with standard CVCs. However, given the paucity of the economic evidence available, the results of these studies must be interpreted carefully. The simple decision model presented here estimated ICERs for a range of different assumptions and demonstrated that all reasonable scenarios show AI-CVCs to be dominant; that is, in terms of cost-effectiveness, they are cheaper and more effective.

However, the limitations of this review should be recognised. Local decisions as to whether or not to adopt AI-CVCs for the prevention of CRBSIs require a clear understanding of the evidence-based reviews and guideline recommendations, as well as knowledge of local clinical practice and infection rates.

Overall, AI-CVCs are clinically effective and relatively inexpensive, and therefore their integration into standard care can be justified. However, the use of these anti-infective catheters without the appropriate use of other practical care

initiatives will have only a limited effect on the prevention of CRBSIs.

Implications for research

It has been estimated that, to take account of all relevant clinical parameters, including mortality, related to the effectiveness of AI-CVCs, a single clinical trial would have to include around 10,000 patients in each study arm. It is highly unlikely that such a trial will ever be funded.

Future trials need to be of a consistently good quality as assessed by Consolidated Standards of Reporting Trials (CONSORT),[100] that is, with true randomisation, and all involved need to be blinded for all relevant information to be monitored and reported (e.g. ITT models, blinding, sample size and powering, confidence intervals). Issues directly related to this subject area include accurate and consistent methods of diagnosis of CRBSI, severity of illness scores, degree of immunosuppression, organisms responsible for colonisation/CRBSI, guidewire exchange, molecular relatedness testing duration of stay, therapeutic antibiotics, occurrence of adverse effects mortality and CVC retention, number of catheters per patient and the number of CRBSI episodes per day at risk.

Comparative trials are required to determine which, if any, of the treated catheters is the most effective.

This review has demonstrated that AI-CVCs can be effective in reducing the number of CRBSIs compared with standard CVCs. Results of the included studies also indicate that rates of CRBSI can be minimised when standard CVCs are used. Therefore, recommendations for pragmatic research related to the effectiveness of bundles of care that may be effective in reducing rates of CRBSI are warranted and should be given the highest priority. Such research will require local audit of CRBSI rates as well as the assessment of current care practices to evaluate the clinical effectiveness and cost-effectiveness of implementing a package of care to reduce CRBSI rates.

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Contribution of authors

Adrian Bagust (Professor of Health Economics) carried out the economic analysis and modelling. Angela Boland (Research Fellow, Health Economics) carried out the economic analysis, evaluated identified economic studies and summarised the economic data. Rumona Dickson (Director of the Liverpool Reviews and Implementation Group) was responsible for the project management and had an input into all aspects of the clinical component of the review. Yenal Dündar (Research Fellow, Clinical Effectiveness) developed the search strategies, assessed the trial quality and had an input into aspects of the clinical component of the review. Kerry Dwan (Medical Statistician) gave statistical advice, carried out data analysis, co-authored the statistical methods and clinical statistical results, and contributed to the writing and editing of drafts of the review. Carrol Gamble (Lecturer in Medical Statistics) gave statistical supervision, co-authored the statistical methods and clinical statistical results sections and provided comments on drafts of the review. Juliet Hockenhull (Research Fellow, Clinical Effectiveness) was responsible for the review's coordination, background, data management and clinical review. Claire McLeod (Research Fellow, Health Economics) carried out the economic data extraction and had an input into all aspects of the economic component of the review. Godfrey Smith (Consultant Microbiologist) gave clinical advice and contributed to writing and editing drafts of the review. Tom Walley (Professor of Pharmacology and Therapeutics) gave clinical advice and commented on the protocol and the final document. All contributors took part in the editing and production of the report.

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Appendix 1

Summary of previous clinical reviews

In preparation for conducting a systematic review on the question of whether AI-CVCs are clinically effective in reducing CRBSI, a literature search of several electronic databases was conducted (full details of the search can be found in Appendix 3).

The literature search highlighted 13 review articles.[2–7,40,101–106] Six of these reviews were systematic reviews of the clinical effectiveness of antimicrobial impregnated/coated CVCs.[2–7] The reasons for exclusion of the remaining seven reviews are shown in *Table 25*.

This appendix summarises the key elements of the six systematic reviews, including time-frames, quality, trials included, the types of catheters analysed, the inclusion and exclusion criteria, data extracted and any issues highlighted by the reviews and conclusions drawn from each review.

Time-frames

The six reviews were published between 1999 and 2003 and conducted their literature searches from 1966. The latest review (Gastmeier, 2003[3]) searched the literature until June 2003. The names of the first authors, publication date and search dates for each of the reviews are shown in *Table 26*.

Data quality

Each of the six reviews were quality assessed using the CRD Checklist for Quality Assessment of Published Reviews.[107] Results of the assessments are shown in *Table 27*.

All reviews asked a well-defined question, had conducted and reported on a thorough literature search and had reported sufficient detail of the individual studies included. However, the quality of inclusion criteria, the validity of included studies and how these studies were combined varied between the reviews.

None of the reviews reported on the number of people applying the inclusion or exclusion criteria, and Pai[6] failed to mention any inclusion or exclusion criteria.

TABLE 25 *Reasons for exclusion*

Review	Reason for exclusion
Geffers, 2003[102]	Review of the methodological quality of the trials available in this area of research
Mermel, 2000[103]	All CRBSI preventive strategies
Zurcher, 2004[106]	Compared single and multilumen CVCs
Saint, 2000[40]	Clinical and economic consequences of nosocomial CVC-related infection
Bambauer, 2004[101]	Narrative overview
Raad, 1999[104]	Narrative overview
Sherertz, 2004[105]	Narrative overview

TABLE 26 *First author, publication date and search dates of each review*

First author	Publication date	Search dates
Veenstra[2]	1999	1966 to January 1998
Marin[4]	2000	1966 to December 1999
Walder[7]	2002	1966 to January 2000
Pai[6]	2001	1966 to September 2000
McConnell[5]	2003	1996 to May 2001
Gastmeier[3]	2003	1966 to June 2003

The validity of included studies was adequately assessed by Veenstra[2] and Walder,[7] but not referred to by Marin[4] or Gastmeier.[3] Pai[6] does discuss the validity of the studies, but not in a systematic manner. McConnell[5] critically reviews the methodology of the 11 trials included in the review, but does not systematically assess the validity of the trials.

Five of the reviews had combined or summarised the primary studies appropriately, but only three of these had investigated the heterogeneity of these studies adequately. McConnell[5] had not combined the studies as he felt this was inappropriate.

In conclusion, two reviews score particularly well (Veenstra[2] and Walder[7]). This may explain the stronger conclusions of these two reviews (*Table 27*).

Included studies

In total, 36 RCTs investigating the efficacy of impregnated or coated CVCs were included. Only eight of these trials were included in all six reviews[50,51,54,56,58,59,63,73] (*Table 28*).

Number of trials/types of catheter

Each review looked at a number of different trials and these trials looked at different types of impregnated or coated CVCs. *Table 29* provides a summary of these trials.

Most reviews looked at trials testing the clinical effectiveness of CHSS-impregnated catheters; only Walder[7] and Pai[6] looked at cuffed or tunnelled catheters. Veenstra[2] was limited to examination of AI-E-CVCs treated with CHSS.

Inclusion/exclusion criteria

All but one review (Pai[6]) reported at least some inclusion/exclusion criteria to substantiate their trial selection (see *Tables 30* and *31*). All included studies were randomised controlled trials. While only one review stated that trials had to be of humans,[4] all included studies were human (two reviews excluded animals).[3,4] The inclusion criteria varied across the six reviews. Reporting of inclusion and exclusion criteria was inconsistent and at times unclear.

Data extraction

Details of the data extracted from trials by each of the reviews are shown in *Table 32*. While some of the different items may in reality be the same, they have been reported here separately so that exactly stated outputs are clear.

Conclusions

The conclusions drawn by each of the reviews are shown in *Table 33*. Any additional notes relevant to these conclusions are also shown.

Four of the reviews conducted meta-analyses, and all four reported a significant reduction in CRBSI when impregnated/coated catheters were used in the short term. All of the reviews mentioned some methodological issues that should be considered. McConnell[5] concluded that the methodological flaws within RCTs were so strong that a combination of data was inappropriate.

Issues raised in the reviews

As mentioned above, some reviews were particularly scathing of the quality of the RCTs

TABLE 27 *Results of the quality assessment on the seven systematic reviews*

Study	Question defined	Search	Inclusion criteria	Validity	Detail	Combined
Veenstra, 1999[2]	Good	Good	Fair	Good	Good	Good
Marin, 2000[4]	Good	Good	Fair	NA	Good	Good
Walder, 2002[7]	Good	Good	Fair	Good	Good	Good
Pai, 2001[6]	Good	Good	NA	Poor	Good	Fair
McConnell, 2003[5]	Good	Good	Fair	Fair	Good	NA
Gastmeier, 2003[3]	Good	Good	Fair	NA	Good	Fair

TABLE 28 *RCTs included in each of the six reviews and the current review*

Study	LRiG	Veenstra, 1999[2]	Marin, 2000[4]	Walder, 2002[7]	Pai, 2001[6]	McConnell, 2003[5]	Gastmeier, 2003[3]
Maki, 1988[75]	Cuff vs non-cuffed			✓	✓		
Flowers, 1989[108]	Cuff vs non-cuffed			✓	✓		
Kamal, 1991[109]	In-house preparation of AI-CVCs			✓	✓		✓
Groeger, 1993[110]	Cuff vs 2nd cuff			✓	✓		
Babycos, 1993[72]	✓						
Bach, 1994[98]	Interim results	✓			✓		
Ramsay, 1994[99]	Interim results	✓			✓		
Dahlberg, 1995[111]	Silver cuff vs non-cuffed			✓			
Goldschmidt, 1995[112]	German			✓	✓		✓
Smith, 1995[113]	Cuff vs non-cuffed			✓	✓		
Trazzera, 1995[114]	Non-RCT	✓			✓		
Appelgren, 1996[115]	Standard CVC vs heparin-bonded CVC		✓				
Bach, 1996[53]	In-house preparation of AI-CVCs			✓	✓		
Bach, 1996[73]	✓	✓	✓	✓	✓	✓	✓
Ciresi, 1996[50]	Not truly random (last digit of records)	✓	✓	✓	✓	✓	✓
Hannan, 1999[63]	Full paper published later	✓					
Pemberton, 1996[54]	✓	✓	✓	✓	✓	✓	✓
Thornton, 1996[116]	In-house preparation of AI-CVCs			✓	✓		
Van Heerden, 1996[55]	✓	✓		✓	✓		
George, 1997[56]	✓	✓	✓	✓	✓	✓	✓
Logghe, 1997[57]	✓		✓	✓	✓	✓	✓
Loo, 1997[117]	Non-RCT			✓	✓		
Maki, 1997[58]	✓	✓	✓	✓	✓	✓	✓
Raad, 1999[104]	✓		✓	✓	✓	✓	✓
Tennenberg, 1997[59]	✓	✓	✓	✓	✓	✓	✓
Heard, 1998[51]	Not truly random (last digit of records)	✓	✓	✓	✓	✓	✓
Trerotola, 1998[60]	✓				✓		
Boswald, 1999[66]	✓			✓			✓
Collin, 1999[62]	✓	✓			✓	✓	✓
Darouiche, 1999[70]	✓				✓		✓
Hannan, 1999[63]	✓		✓	✓	✓	✓	✓
Bach, 1999[61]	✓						
Marik, 1999[71]	✓			✓	✓		✓
Moss, 2000[67]	✓						✓
Sheng, 2000[64]	✓						✓
Jaeger, 2001[68]	✓						
Stoiser, 2002[69]	✓						✓
Theaker, 2002[65]	✓						✓
Ranucci, 2003[17]	✓						✓
Bong, 2003[16]	✓						
Corral, 2003[14]	✓						
Chatzinikolaou, 2003[15]	✓						
Brun-Buisson, 2004[13]	✓						
Carrasco, 2004[12]	✓						
Hanna, 2004[11]	✓						
Leon, 2004[10]	✓						
Yücel, 2004[9]	✓						
Jaeger, 2005[8]	✓						
Rupp, 2005[18]	✓						

TABLE 29 *Total number of trials and the number of trials evaluating each type of catheter as considered by each review*

Types of catheter	Veenstra, 1999[2]	Marin, 2000[4]	Walder, 2002[7]	Pai, 2001[6]	McConnell, 2003[5]	Gastmeier, 2003[3]
No. of trials	13	11	23	27	11	21
CHSS	13	11	12	17	10	12
Silver impregnated			2	2		5
Benzalkonium chloride						2
Chlorhexidine only						1
MR		1	1	3	1	3
Cefazolin				1		1
Teicoplanin				1		
Vancomycin				1		
Heparinised		1				
Bath (various)			3			
Cuffed/tunnelled			5	4		

TABLE 30 *Inclusion criteria of each review*

	Veenstra, 1999[2]	Marin, 2000[4]	Walder, 2002[7]	Pai, 2001[6]	McConnell, 2003[5]	Gastmeier, 2003[3]
RCT	✓	✓	✓		✓	✓
Human		✓				✓
Controls are standard CVCs	✓		✓		✓	
Articles			✓		✓	
CHSS	✓					
Colonisation or CRBSI	✓					
Inserted percutaneously			✓			
Colonisation per 100 catheters or BSI per 100 catheters			✓			

TABLE 31 *Exclusion criteria of each review*

	Veenstra, 1999[2]	Marin, 2000[4]	Walder, 2002[7]	Pai, 2001[6]	McConnell, 2003[5]	Gastmeier, 2003[3]
Animal		✓				✓
In vitro						✓
Abstracts only						✓
Colonisation only						✓
Impregnated cuffs only						✓
Children (<17 years)		✓				
Exchanged over a guidewire			✓			

reviewed. Below are some of the issues that were raised by the reviews. Future trials would need to address these methodological flaws:

- diagnosis of CRBSI – definitions
- CRI rates in different patient groups
- missing key confounding variables
- severity of illness scores
- degree of immunosuppression
- organisms responsible for colonisation/CRBSI
- inclusion of arterial CVCs
- inclusion of guidewire exchange
- reporting of ITT models
- reporting of blinding
- reporting of sample size and powering
- reporting of confidence intervals
- lack of molecular relatedness testing
- limited reporting of clinically relevant end-points, such as duration of stay, therapeutic antibiotics, occurrence of adverse effects, mortality and CVC retention
- number of catheters per patient
- none of the studies looked at by McConnell evaluated the number of CRBSI episodes per day at risk.

TABLE 32 *Data extracted by each of the reviews*

Extracted	Veenstra, 1999[2]	Marin, 2000[4]	Walder, 2002[7]	Pai, 2001[6]	McConnell, 2003[5]	Gastmeier, 2003[3]
Authors	✓	✓	✓	✓		✓
Year of publication	✓	✓	✓	✓		✓
Setting in which study was performed	✓	✓	✓		✓	✓
Study design				✓		
Total no. of patients	✓	✓		✓	✓	
Age of patients				✓		
Quality assessment			✓			
Study methodologies					✓	
Reference source		✓				
Diagnosis criteria for CRBSI	✓					✓
Diagnosis criteria for colonisation	✓					✓
No. of catheters	✓	✓	✓	✓	✓	✓
Catheter type experimental		✓	✓	✓	✓	✓
Catheter type control		✓	✓	✓	✓	✓
No. of lumens	✓		✓	✓		
Average duration of catheter use	✓		✓	✓	✓	✓
Catheter exchange using a guidewire	✓					
Relative colonisation risk			✓			✓
Relative CRBSI risk			✓			✓
No. of catheters associated with colonisation	✓		✓	✓	✓	
No. of catheters associated with BSI	✓		✓	✓	✓	
No. of catheters used without infections		✓				
Efficacy rate of CVCs in prevention of CRBSI					✓	
Organisms infecting the catheters		✓				
Organisms cultured in BSI catheters		✓			✓	
Whether catheter-related complications occurred		✓			✓	

TABLE 33 *Review conclusions*

Study	Reduce CRBSI	Notes
Veenstra, 1999[2]	Yes	40% reduction applicable if patient population is consistent, high risk, short-term use of multilumen CVC
Marin, 2000[4]	Yes	Also conclude that they are also cost-effective
Walder, 2002[7]	Yes	Short term effective (<1 week). Lack of evidence for longer term. No evidence for cuffs
Pai, 2001[6]	No meta-analysis	Based on Veenstra (1999)[2] concluded that CHSS effective in short term and AI-CVCs treated with MR reduce CRBSI, as all trials were significant
		MR superior to CHSS (in short term)
McConnell, 2003[5]	No meta-analysis	Too many methodological flaws in trials to be confident of any results
Gastmeier, 2003[3]	Yes, but only in the short term	Inconclusive
		Too few trials on catheters impregnated/coated with anti-infective agents other than CHSS
		CHSS reduced CRBSI if short-term catheterisation (<8 days) were included
		Methodological flaws of trials

Appendix 2

Department of Health EPIC guidelines

TABLE 34 *Recommendations for preventing CVC-associated infections*[25]

Education of healthcare workers and patients		
CVAD 1	Healthcare workers caring for a patient with a central venous access device should be trained, and assessed as competent in using and consistently adhering to the infection prevention practices described in this guideline.	Class D
CVAD 2	Before discharge from hospital, patients with a central venous access device and their carers should be taught any techniques they may need to use to prevent infection and safely manage their device.	Class D/ GPP
General asepsis		
CVAD 3	An aseptic non-touch technique (ANTT) must be used for catheter site care and for accessing the system.	Class B
CVAD 4	Before accessing or dressing a central venous access device, hands must be decontaminated either by washing with an antimicrobial liquid soap and water, or by using an alcohol handrub.	Class A
CVAD 5	Hands that are visibly soiled or contaminated with dirt or organic material must be washed with liquid soap and water before using an alcohol handrub.	Class A
CVAD 6	Following hand antisepsis, clean gloves and an ANTT, or sterile gloves should be used when changing the insertion site dressing, line manipulation or intravenous drug administration.	Class D
Selection of catheter type		
CVAD 7	Use a single-lumen catheter unless multiple ports are essential for the management of the patient.	Class A
CVAD 8	If a multilumen catheter is used, identify and designate one port exclusively for hyperalimentation to administer parenteral nutrition.	Class D/ GPP
CVAD 9	Use a tunnelled or implanted central venous access device (one with a subcutaneous port) for patients in whom long-term (more than 3–4 weeks) vascular access is anticipated.	Class A
CVAD 10	Consider the use of an antimicrobial impregnated central venous access device for adult patients who require short-term (1–3 weeks) central venous catheterisation and who are at high risk for catheter-related bloodstream infection (CR-BSI) if rates of CR-BSI remain high despite implementing a comprehensive strategy to reduce rates of CR-BSI.	Class A
Selection of catheter insertion site		
CVAD 11	In selecting an appropriate insertion site, assess the risks for infection against the risks of mechanical complications.	Class D/ GPP
CVAD 12	Unless medically contraindicated, use the subclavian site in preference to the jugular or femoral sites for non-tunnelled catheter placement.	Class C
CVAD 13	Use implantable access devices for patients who require long-term, intermittent vascular access. For patients requiring regular or continuous access, a tunnelled central venous access device is preferable.	Class C
Maximal sterile barrier precautions during catheter insertion		
CVAD 14	Use maximal sterile barriers, including a sterile gown, sterile gloves and a large sterile drape, for the insertion of central venous access devices.	Class C

continued

TABLE 34 *Recommendations for preventing CVC-associated infections[25] (cont'd)*

	Cutaneous antisepsis	
CVAD 15	Decontaminate the skin site with a single patient use application of alcoholic chlorhexidine gluconate solution (preferably 2% chlorhexidine gluconate in 70% isopropyl alcohol) prior to the insertion of a central venous access device.	Class A
CVAD 16	Use a single patient use application of alcoholic povidone-iodine solution for patients with a history of chlorhexidine sensitivity. Allow the antiseptic to dry before inserting the central venous access device.	Class D/ GPP
CVAD 17	Do not apply organic solvents, e.g. acetone, ether, to the skin before the insertion of a central venous access device.	Class D/ GPP
CVAD 18	Do not routinely apply antimicrobial ointment to the catheter placement site prior to insertion.	Class D/ GPP
	Catheter and catheter site care	
CVAD 19	Preferably, a sterile, transparent, semi-permeable polyurethane dressing should be used to cover the catheter insertion site.	Class D
CVAD 20	Transparent dressings should be changed every 7 days, or sooner if they are no longer intact or moisture collects under the dressing.	Class D
CVAD 21	If a patient has profuse perspiration or if the insertion site is bleeding or oozing, a sterile gauze dressing is preferable to a transparent, semi-permeable dressing.	Class D/ GPP
CVAD 22	The need for a gauze dressing should be assessed daily and changed when inspection of the insertion site is necessary or when the dressing becomes damp, loosened or soiled. A gauze dressing should be replaced by a transparent dressing as soon as possible.	Class D/ GPP
CVAD 23	Dressings used on tunnelled or implanted catheter insertion sites should be replaced every 7 days until the insertion site has healed, unless there is an indication to change them sooner.	Class D
CVAD 24	An alcoholic chlorhexidine gluconate solution (preferably 2% chlorhexidine gluconate in 70% isopropyl alcohol) should be used to clean the catheter insertion site during dressing changes, and allowed to air dry. An aqueous solution of chlorhexidine gluconate should be used if the manufacturer's recommendations prohibit the use of alcohol with their product.	Class A
CVAD 25	Individual single use sachets of antiseptic solution or individual packages of single use antiseptic-impregnated swabs or wipes should be used to disinfect the insertion site.	Class D/ GPP
CVAD 26	Do not apply antimicrobial ointment to catheter insertion sites as part of routine catheter site care.	Class D/ GPP
CVAD 27	Healthcare workers should ensure that catheter-site care is compatible with catheter materials (tubing, hubs, injection ports, luer connectors and extensions) and carefully check compatibility with the manufacturer's recommendations.	Class D/ GPP
	Catheter replacement strategies	
CVAD 28	Do not routinely replace catheters as a method to prevent catheter-related infection.	Class A
CVAD 29	Use guidewire assisted catheter exchange to replace a malfunctioning catheter, or to exchange an existing catheter only if there is no evidence of infection at the catheter site or proven catheter-related bloodstream infection.	Class A
CVAD 30	If catheter-related infection is suspected, but there is no evidence of infection at the catheter site, remove the existing catheter and insert a new catheter over a guidewire; if tests reveal catheter-related infection, the newly inserted catheter should be removed and, if still required, a new catheter inserted at a different site.	Class A
CVAD 31	Do not use guidewire assisted catheter exchange for patients with catheter-related infection. If continued vascular access is required, remove the implicated catheter, and replace it with another catheter at a different insertion site.	Class A
CVAD 32	Replace all fluid administration tubing and connectors when the central venous access device is replaced.	Class D/ GPP

continued

TABLE 34 *Recommendations for preventing CVC-associated infections[25] (cont'd)*

	General principles for catheter management	
CVAD 33	A single patient use application of alcoholic chlorhexidine gluconate solution (preferably 2% chlorhexidine gluconate in 70% isopropyl alcohol) should be used and allowed to dry when decontaminating the injection port or catheter hub before and after it has been used to access the system, unless contraindicated by the manufacturer's recommendations, in which case either aqueous chlorhexidine gluconate or aqueous povidone iodine should be used.	Class D/ GPP
CVAD 34	In-line filters should not be used routinely for infection prevention purposes.	Class D
CVAD 35	Antibiotic lock solutions should not be used routinely to prevent catheter-related bloodstream infections.	Class D
CVAD 36	Do not routinely administer intranasal or systemic antimicrobials before insertion or during the use of a central venous access device to prevent catheter colonisation or bloodstream infection.	Class A
CVAD 37	Preferably, a single-lumen catheter should be used to administer parenteral nutrition. If a multilumen catheter is used, one port must be exclusively dedicated for hyperalimentation and all lumens must be handled with the same meticulous attention to aseptic technique.	Class D
CVAD 38	Preferably, sterile 0.9% sodium chloride for injection should be used to flush and lock catheter lumens that are in frequent use.	Class A
CVAD 39	When recommended by the manufacturer, implanted ports or opened-ended catheter lumens should be flushed and locked with heparin sodium flush solutions.	Class D
CVAD 40	Systemic anticoagulants should not be used routinely to prevent catheter-related bloodstream infection.	Class D
CVAD 41	The introduction of new intravascular devices that include needle-free devices should be monitored for an increase in the occurrence of device-associated infection. If an increase in infection rates is suspected, this should be reported to the Medicines and Healthcare products Regulatory Agency [http://www.mhra.gov.uk]	Class D/ GPP
CVAD 42	If needle-free devices are used, the manufacturer's recommendations for changing the needle-free components should be followed.	Class D/ GPP
CVAD 43	When needle-free devices are used, healthcare workers should ensure that all components of the system are compatible and secured, to minimise leaks and breaks in the system.	Class D/ GPP
CVAD 44	When needle-free devices are used, the risk of contamination should be minimised by decontaminating the access port before and after use with a single patient use application of alcoholic chlorhexidine gluconate solution (preferably 2% chlorhexidine gluconate in 70% isopropyl alcohol) unless contraindicated by the manufacturer's recommendations, in which case aqueous povidone iodine should be used.	Class D
CVAD 45	In general, solution administration sets in continuous use need not be replaced more frequently than at 72-hour intervals unless they become disconnected or a central venous access device is replaced.	Class A
CVAD 46	Administration sets for blood and blood components should be changed when the transfusion episode is complete or every 12 hours (whichever is sooner), or according to the manufacturer's recommendations.	Class D
CVAD 47	Administration sets used for total parenteral nutrition infusions should generally be changed every 24 hours. If the solution contains only glucose and amino acids, administration sets in continuous use do not need to be replaced more frequently than every 72 hours.	Class D

continued

TABLE 34 *Recommendations for preventing CVC-associated infections[25] (cont'd)*

Class	*Evidence*
A	At least one meta-analysis, systematic review, or randomised controlled trial (RCT) that is rated as 1++, and is directly applicable to the target population, or
	A systematic review of RCT or a body of evidence that consists principally of studies rated as 1+, is directly applicable to the target population and demonstrates overall consistency of results
	Evidence drawn from a NICE technology appraisal
B	A body of evidence that includes studies rated as 2++, is directly applicable to the target population and demonstrates overall consistency of results, or
	Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence that includes studies rated as 2+, is directly applicable to the target population and demonstrates overall consistency of results, or
	Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4, or
	Extrapolated evidence from studies rated as 2+, or
	Formal consensus
D (GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the Guideline Development Group
IP	Recommendation from NICE Interventional Procedures guidance.

Appendix 3

Search strategies and search results

TABLE 35 *Search for clinical effectiveness studies: summary*

Database	Years	Search strategy	References identified
MEDLINE	1985–2005	See below	464
EMBASE	1985–2005	See below	311
Science Citation Index/Web of Science	1985–2005	(central venous catheter* and infect* and (trial* or stud*))	436
Science Citation Index/ ISI Proceedings	1990–2005	As above	54
Cochrane Central	1985–2005	As above	273
HTA[a]	1985–2005	As above	2
DARE[a]	1985–2005	As above	17
	Total references identified		1557
	Duplicates		687
	Total		871

[a] These databases have retrospective coverage of literature a few years prior to the start dates given. Also, the HTA used to be included as part of the DARE.

TABLE 36 *Search for cost-effectiveness studies: summary*

Database	Years	Search strategy	References identified
MEDLINE (OVID)	1966 to week 3 2005	1 exp Catheters, Indwelling/ or exp Catheterization, Central Venous/ or central venous catheter.mp. (17137) 2 cost.mp. or exp "Costs and Cost Analysis"/ (186813) 3 1 and 2 (569) 4 infection control.mp. or exp Infection Control/ (37342) 5 exp Anti-Infective Agents/ or anti-infective.mp. (855045) 6 1 and 2 and (4 or 5) (127) 7 from 6 keep 1–10 (10) 8 from 6 keep 1–127 (127)	127
Science Citation Index/Web of Science	1987–2005	"venous and catheter and cost and infection"	53
Science Citation Index/ ISI Proceedings	1987–2005	"venous and catheter and cost and infection"	5
NHS EED (The Cochrane Library)	2005 (4)	"venous and catheter and cost and infection"	29
HTA (The Cochrane Library)	2005 (4)	"venous and catheter and cost and infection"	0
	Identified from handsearching and clinical review of effectiveness		5
	Total references identified		219
	Duplicates		41
	Total		182

MEDLINE 1985–2005

1985 to July week 3 2005

1. randomized controlled trial.pt.
2. randomized controlled trials/
3. random allocation/
4. controlled clinical trial.pt.
5. double-blind method/
6. single-blind method/
7. or/1-6
8. Animal/ not Human/
9. 7 not 8
10. clinical trial.pt.
11. exp clinical trials/
12. (clinic$ adj25 trial$).tw.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
14. placebos/
15. (placebo$ or random$).tw.
16. research design/
17. or/10-16
18. 17 not 8
19. 18 not 9
20. 9 or 19
21. exp Catheterization, Central Venous/
22. (CATHETER$ and VENOUS).tw.
23. (central adj3 catheter).tw.
24. or/21-23
25. exp Anti-Infective Agents/
26. exp Infection Control/
27. (catheter$ adj25 infect$).tw.
28. or/25-27
29. 24 and 28
30. 20 and 29
31. limit 30 to yr="1985 - 2005" (464 hits)

EMBASE 1985–2005

1985 to 2005 week 31

1 exp central venous catheter/
2 (CATHETER$ and VENOUS).tw.
3 (central adj3 catheter).tw.
4 or/1-3
5 exp Antiinfective Agent/
6 exp Catheter Infection/
7 exp Infection Risk/
8 (catheter$ adj25 infect$).tw.
9 or/5-8
10 4 and 9
11 random$.ti,ab.
12 factorial$.ti,ab.
13 (crossover$ or cross over$ or cross-over$).ti,ab.
14 placebo$.ti,ab.
15 (double$ adj blind$).ti,ab.
16 (singl$ adj blind$).ti,ab.
17 assign$.ti,ab.
18 allocat$.ti,ab.
19 volunteer$.ti,ab.
20 Crossover Procedure/
21 Double Blind Procedure/
22 Randomized Controlled Trial/
23 Single Blind Procedure/
24 or/11-23
25 exp animal/
26 nonhuman/
27 exp animal experiment/
28 or/25-27
29 exp human/
30 28 not 29
31 24 not 30
32 10 and 31
33 limit 32 to yr="1985 – 2005"

Appendix 4

Quality assessment for clinical studies

Studies of clinical effectiveness will be assessed using the following criteria, based on CRD Report No. 4, University of York.[44]

- Was the method used to assign participants to the treatment groups really random? (Computer-generated random numbers and random number tables will be accepted as adequate, whereas inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week.)
- Was the allocation of treatment concealed? (Concealment will be deemed adequate where randomisation is centralised or pharmacy controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes, even if opaque.)
- Was the number of participants who were randomised stated?
- Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Was baseline comparability achieved for treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Were the eligibility criteria for study entry specified?
- Were any co-interventions identified that may influence the outcomes for each group?
- Were the outcome assessors blinded to the treatment allocation?
- Were the individuals who were administered the intervention blinded to the treatment allocation?
- Were the participants who received the intervention blinded to the treatment allocation?
- Was the success of the blinding procedure assessed?
- Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
- Were the reasons for any withdrawals stated?
- Was an intention-to-treat analysis included?

Items were graded as: ✓, yes (item adequately addressed); ✗, no (item not adequately addressed); ✓/✗, partially (item partially addressed); NA, not applicable; or NS, not stated.

Appendix 5

Additional information from authors

The data extraction for this report is also being utilised in another project. For reasons pertinent to this additional project seven authors were contacted. As these seven authors were being contacted they were also asked to clarify missing information from the published trials that were pertinent to this review. Replies were received from four of the seven authors contacted. The information they were asked for is shown in *Table 37* and specific questions per author are indicated by shaded boxes. Each box contains the author's reply.

TABLE 37 *Information received via correspondence with authors*

Variable	Hanna[11]	Logghe[57]	Trerotola[60]	Van Heerden[55]
Data quality assessment				
Method of randomisation		Permutation table	Random number generator	Flipped a coin
Allocation concealment		Yes		No
Blinding of assessors		No	No; differences too obvious	No
Blinding of administrators	No different colour		No; differences too obvious	No
Blinding of patients			No; differences too obvious	No
Data extraction				
When study conducted				1995/1996
Same arm		No		
Age				
Reason for CVC				
Illness				Various
Site				Subclavian and internal jugular
No catheter exchange using a guidewire	None		None	
Reason for removal				
Inserted by	Surgeons, subclavian and trained infusion; therapy nurse, PICC			Medical staff, registrars and consultants
Skin preparation	10% povidone iodine			
Dressing type		Plain gauze		

Appendix 6

Clinical: excluded references

TABLE 38 *Details of trials excluded from the review*

Trial reference	Reason for exclusion
Appelgren P, Ransjo U, Bindslev L, Espersen F, Larm O. Surface heparinization of central venous catheters reduces microbial colonization *in vitro* and *in vivo*: results from a prospective, randomized trial. *Crit Care Med* 1996;**24**:1482–9.	Standard CVC vs heparin-bonded CVC
Bach A, Bohrer H, Bottiger BW, Motsch J, Martin E. Reduction of bacterial colonization of triple-lumen catheters with antiseptic bonding in septic patients [abstract]. *Anesthesiology* 1994;**81**:a261.	Interim results
Bach A, Darby D, Bottiger B, Bohrer H, Motsch J, Martin E. Retention of the antibiotic teicoplanin on a hydromer-coated central venous catheter to prevent bacterial colonization in postoperative surgical patients. *Intensive Care Med* 1996;**22**:1066–9.	In-house preparation of AI-CVCs
Barbosa D, Pignatari A, Draibe S, Sader H, Leme I, Manfredi S, *et al*. A randomized trial evaluating topical mupirocin for the prevention of infections related to central venous catheters for hemodialysis [abstract]. *J Am Soc Nephrol* 1997;**8**:152a.	In-house preparation of AI-CVCs
Ciresi DL, Albrecht RM, Volkers PA, Scholten DJ, Senagore A, Bodzin JH, *et al*. Failure of antiseptic bonding to prevent central venous catheter-related infection and sepsis. *Am Surg* 1996;**62**:641–6.	Not truly random (randomised by last digit of patient's medical records)
Crabtree JH, Burchette RJ, Siddiqi RA, Huen LL, Hadnott LL, Fishman A. Efficacy of silver-ion implanted catheters in reducing peritoneal dialysis-related infections. *Perit Dial Int* 2003; **23**:368–74.	Peritoneal catheters
Dahlberg PJ, Agger WA, Singer JR, Yutuc WR, Newcomer KL, Schaper A, *et al*. Subclavian hemodialysis catheter infections: a prospective, randomized trial of an attachable silver-impregnated cuff for prevention of catheter-related infections. *Infect Control Hosp Epidemiol* 1995;**16**:506–11.	Silver cuff vs non-cuffed
Flowers RH III, Schwenzer KJ, Kopel RF, Fisch MJ, Tucker SI, Farr BM. Efficacy of an attachable subcutaneous cuff for the prevention of intravascular catheter-related infection. A randomized, controlled trial. *JAMA* 1989;**261**:878–83.	Cuff vs non-cuffed
Groeger JS, Lucas AB, Coit D, Laquaglia M, Brown AE,Turnbull A, *et al*. A prospective, randomized evaluation of the effect of silver impregnated subcutaneous cuffs for preventing tunneled chronic venous access catheter infections in cancer patients. *Ann Surg* 1993; **218**:206–10.	Cuff vs 2nd cuff
Hannan M, Just R, Shankar, U, Nightingale C, Azadin B, Soni N. Colonization of triple lumen catheters. A study on antiseptic bonded and standard catheters. *Clin Intensive Care* 1996;**7**:56.	Full paper published later
Heard SO, Wagle M, Vijayakumar E, Mclean S, Brueggemann A, Napolitano LM, *et al*. Influence of triple-lumen central venous catheters coated with chlorhexidine and silver sulfadiazine on the incidence of catheter-related bacteremia. *Arch Intern Med* 1998;**158**:81–7.	Not truly random (randomised by last digit of patient's medical records)
Kamal GD, Pfaller MA, Rempe LE, Jebson PJR. Reduced intravascular catheter infection by antibiotic bonding. A prospective, randomized, controlled trial. *JAMA* 1991;**265**:2364–8.	In-house preparation of AI-CVCs
Leon C, Alvarez-Lerma F, Ruiz-Santana S, Gonzalez V, De La Torre MV, Sierra R, *et al*. Antiseptic chamber-containing hub reduces central venous catheter-related infection: a prospective, randomized study. *Crit Care Med* 2003;**31**:1318–24.	Antiseptic chamber containing hub vs standard Luer-Lok connector
Maki DG, Cobb L, Garman JK, Shapiro JM, Ringer M. Helgerson RB. An attachable silver-impregnated cuff for prevention of infection with central venous catheters – a prospective randomized multicenter trial. *Am J Med* 1988;**85**:307–14.	Cuff vs non-cuffed
Pierce CM, Wade A, Mok Q. Heparin-bonded central venous lines reduce thrombotic and infective complications in critically ill children. *Intens Care Med* 2000;**26**:967–72.	Standard CVC vs heparin-bonded CVC

continued

TABLE 38 *Details of trials excluded from the review (cont'd)*

Trial reference	Reason for exclusion
Raad I, Costerton W, Sabharwal U, Sacilowski M, Anaissie E, Bodey GP. Ultrastructural analysis of indwelling vascular catheters – a quantitative relationship between luminal colonization and duration of placement. *J Infect Dis* 1993;**168**:400–7.	Subgroup of a later and included study
Ramsay J, Nolte F, Schwarzmann S. Incidence of catheter colonization and catheter related infection with an antiseptic impregnated triple lumen catheter [abstract]. *Crit Care Med* 1994; **22**:A115.	Interim data
Smith HO, Devictoria CL, Garfinkel D, Anderson P, Goldberg GL, Soeiro R, *et al*. A prospective randomized comparison of an attached silver-impregnated cuff to prevent central venous catheter-associated infection. *Gynecol Oncol* 1995;**58**:92–100.	Cuff vs non-cuffed
Thornton J, Todd NJ, Webster NR. Central venous line sepsis in the intensive care unit – a study comparing antibiotic coated catheters with plain catheters. *Anaesthesia* 1996; **51**:1018–20.	In-house preparation of AI-CVCs
Trazzera S, Stern G, Bhardwaj R, Sinha S, Reiser P. Examination of antimicrobial coated central venous catheters in patients at high risk for catheter related infections in a medical intensive care unit and leukemia/bone marrow transplant unit. *Crit Care Med* 1995;**23**:A152.	Non-RCT
Van Vliet J, Leusink JA, De Jongh BM, De Boer A. A comparison between two types of central venous catheters in the prevention of catheter-related infections: the importance of performing all the relevant cultures. *Clin Intensive Care* 2001;**12**:135–40.	Not truly random (randomised by alternate days)

Appendix 7

Reported outcomes for clinical studies

TABLE 39 *Reported rates of CRBSI for standard and AI-CVCs*

Trial	CRBSI							CRBSI 2[a]						
	AI-CVC			Standard			Category	AI-CVC			Standard			Category
	n	*N*	%	*n*	*N*	%		*n*	*N*	%	*n*	*N*	%	
Babycos, 1993[72]	0	17	0	1	16	6	βS+	[b]						
Bach, 1996[53]	0	116	0	3	117	3	αS–							
Pemberton, 1996[54]	2	32	6	3	40	8	βS–							
Van Heerden, 1996[55]														
George, 1997[56]														
Logghe, 1997[57]	17	338		15	342		βSX	49	338	14	56	342	16	θ
Maki, 1997[58]	2	72	3	7	86	8	αS+							
Raad, 1997[38]	0	130	0	5	136	4	αS+	0	130	0	7	136	5	βS+
Tennenberg, 1997[59]	5	137	4	9	145	6	βS+							
Trerotola, 1998[60]														
Bach, 1999[61]														
Boswald, 1999[66]	4	86	5	13	79	16	βS+							
Collin, 1999[62]	1	98	1	4	139	3	βS+							
Darouiche, 1999[70]	1	356	0.3	13	382	3	βS+							
Hannan, 1999[63]	1	174	1	3	177	2	βS–							
Marik, 1999[71]	1	36	3	1	20	5	βS–							
Marik, 1999[71]	0	38	0	1	19	5	βS–							
Moss, 2000[67]														
Sheng, 2000[64]	1	113	1	2	122	2	βS+							
Jaeger, 2001[68]	1	25	4	1	25	4	βS–							
Stoiser, 2002[69]	3	50	6	3	47	6	βS+							
Theaker, 2002[65]														
Bong, 2003[16]	7	128	5	11	142	8	αS+							
Chatzinikolaou, 2003[15]	0	66	0	7	64	11	βS+							
Corral, 2003[14]	1	103	1	4	103	4	βS+							
Ranucci, 2003[17]	9	268	3	12	277	4	βS+							
Brun-Buisson, 2004[13]	3	188	2	5	175	3	βS+							
Carrasco, 2004[12]	3	128	2	4	132	3	βS–							
Hanna, 2004[11]	3	182	2	14	174	8	βSX							
Leon, 2004[10]	6	187	3	11	180	6	βS+							
Yücel, 2004[9]	0	118	0	1	105	1	βS+							
Jaeger, 2005[8]	1	51	2	8	55	15	βS–							
Rupp, 2005[18]	1	345	0	3	362	1	βS+							

[a] Some studies had information for more than one kind of definition of CRBSI.
[b] Blank squares indicate that this outcome was not reported.

TABLE 40 *Reported rates of colonisation for standard and AI-CVCs*

Trial	Colonisation 1							Colonisation 2							Colonisation 3						
	AI-CVC			Standard			Category	AI-CVC			Standard			Category	AI-CVC			Standard			Category
	n	*N*	%	*n*	*N*	%		*n*	*N*	%	*n*	*N*	%		*n*	*N*	%	*n*	*N*	%	
Babycos, 1993[72]																					
Bach, 1996[53]	21	116	18	36	117	31	D														
Pemberton, 1996[54]																					
Van Heerden, 1996[55]	4	28	14	10	26	38	A														
George, 1997[56]	10	44	23	25	35	71	D														
Logghe, 1997[57]																					
Maki, 1997[58]	28	208	13	47	195	24	A														
Raad, 1997[38]	11	130	8	36	136	26	A or C														
Tennenberg, 1997[59]	8	137	6	32	145	22	A														
Trerotola, 1998[60]	8	47	17	7	44	16	A														
Bach, 1999[61]	6	34	18	3	33	9	C														
Boswald, 1999[66]	12	86	14	17	79	22	A														
Collin, 1999[62]	1	98	1	4	139	3	A	2	98	2	25	139	18	D							
Darouiche, 1999[70]	28	356	8	87	382	23	A or C														
Hannan, 1999[63]	47	174	27	71	177	40	C														
Marik, 1999[71]	7	36	19	6	20	30	A														
Marik, 1999[71]	4	38	11	5	19	26	A														
Moss, 2000[67]	18	106	17	25	98	26	D														
Sheng, 2000[64]	9	113	8	25	122	20	A														
Jaeger, 2001[68]	4	25	16	4	25	16	A														
Stoiser, 2002[69]	10	50	20	14	47	30	A or C														
Theaker, 2002[65]	40	101	40	55	131	42	A														
Bong, 2003[16]	47	128	37	48	142	34	A or B														
Chatzinikolaou, 2003[15]	13	66	20	16	64	25	C														
Corral, 2003[14]	15	103	15	29	103	28	A														
Ranucci, 2003[17]	42	268	16	71	277	26	A or C														
Brun-Buisson, 2004[13]	7	188	4	23	175	13	C														
Carrasco, 2004[12]	13	128	10	29	132	22	A or C														
Hanna, 2004[11]																					
Leon, 2004[10]	20	187	11	45	180	25	A	17	187	9	34	180	19	C							
Yücel, 2004[9]	6	118	5	38	105	36	A	7	118	6	41	105	39	C	7	118	6	41	105	39	A or C
Jaeger, 2005[8]	5	51	10	9	55	16	A														
Rupp, 2005[18]	32	345	9	59	362	16	A or C														

Appendix 8

Study characteristics

TABLE 41 *Study characteristics*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Babycos, 1993[72]	Control	Monitoring, blood sampling, transfusions, infusions, medications, TPN		Pneumonia + HIV = 1 Liver failure = 2 Gastric outlet obstruction = 1 Decubitus = 2 Cerebrovascular accident = 1 Carcinomatosis = 2 Lung cancer = 1 Oesophageal cancer = 1 Liver cancer = 1 Pancreatic pseudocyst = 1 Osteogenic sarcoma = 1	Surgical, required CVCs	Under 18 Acute trauma patients whose catheters were inserted in the emergency room Pregnancy Sepsis of no known source	CVC sepsis	Insertion site infection		3	Asepsis	
	Treatment			Decubitus/sepsis = 2 Lung cancer = 2 Upper gastrointestinal haemorrhage = 1 Oesophageal cancer = 1 Coronary artery disease = 1 Gastric cancer = 1 Pancreatic abscess = 1 Toxic megacolon = 1 Crohn's disease=1 Pneumonia=1 Gastris outlet obstruction = 1								

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Bach, 1996[53]		Cardiac surgery			Cardiac surgery Non-pregnant, non-lactating patients Over the age of 18 years Due to receive a double- or triple-lumen catheter	History of adverse reactions to silver, sulfonamides or chlorhexidine Immune deficiency Needed additional intravascular access (with the exception of an arterial line)	Level of antimicrobial activity that was retained on the surface of these catheters after various periods of i.v. catheterisation	Bacterial colonisation		2 or 3		
Pemberton, 1996[54]	Control	TPN		Pancreatic disease = 13 Cancer = 5 Bowel obstruction = 7 Bowel surgery = 7 Other = 8	Inpatients on the metabolic support service received a CVC for the infusion of TPN	Patients who had a higher risk for contamination during insertion, such as those with a catheter placed through an introducer, inserted in the emergency department, or changed over a guidewire into the same infected site, or any patient with a history of an allergy to sulfa drugs	Catheter sepsis, catheter site infection	Mortality, micro-organisms		3		
	Treatment			Pancreatic disease = 9 Cancer = 4 Bowel obstruction = 4 Bowel surgery = 4 Other = 11								

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Van Heerden, 1996[55]	Treatment	Drug administration, TPN, monitoring purposes		Various[a]	Requiring central venous lines for drug administration, parental nutrition or monitoring purposes and who were expected to have the device *in situ* for ⩾5 days		Presence of infection, colonisation. To determine whether the FAS brush was able to detect infection early (day 3) within the CVC	Organisms		3		End of study
George, 1997[56]	Control	Thoracic organ transplantation with concomitant immuno-suppression		Orthotropic heart transplant = 13 Heterotopic heart transplant = 6 Lung transplant = 12 Heart–lung transplant = 4	Patients undergoing or having undergone transplantation of the heart, heart–lungs or lung(s) with concomitant immuno-suppression, requiring venous access		Colonisation	Associated infection		Multiple		Signs of local infection Positive blood cultures requiring a change of lines Clinical decision
	Treatment			Orthotropic heart transplant = 15 Heterotopic heart transplant = 7 Lung transplant = 15 Heart–lung transplant = 6						Standard aseptic non-touch protocol		

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Logghe, 1997[57]	Control	Chemotherapy		Leukaemia = 208 Lymphoma = 61 Myeloma = 46 Dysplasia = 10 Hodgkin = 6 Other = 11	With a haematological malignancy with treatment administered by CVC		Bacteraemia, catheter-related bacteraemia	Residual antiseptic activity	80%	Multiple		End of treatment Mechanical problems Failure to treat BSI
	Treatment			Leukaemia = 201 Lymphoma = 54 Myeloma = 43 Dysplasia = 15 Hodgkin = 10 Other = 15								
Maki, 1997[58]					All adult patients who were not known to be allergic to chlorhexidine, silver or sulfonamides and were scheduled to receive CVC for short-term use		Prevention of CRBSI and colonisation	Resistance to CHSS		3		

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Raad, 1997[38]	Control	Chemotherapy, TPN, administration of blood products	122	Cancer = 34 Cardiopulmonary disease = 37 Neurosurgery or head trauma = 36 Abdominal surgery = 36 Other = 8	Hospitalised patients ⩾18 years of age who required a triple-lumen polyurethane CVC at a new insertion site	Pregnant women, patients who were allergic to rifampin or tetracycline, patients with dermatitis or a burn over the insertion site and patients for whom the anticipated duration of catheterisation was <3 days	Colonisation	BSIs		3	Aseptic	No longer needed = 109 Suspected infection = 18 Clotted catheter or thrombosis = 1 Other = 23
	Treatment		123	Cancer = 35 Cardiopulmonary disease = 40 Neurosurgery or head trauma = 32 Abdominal surgery = 30 Other = 10								No longer needed = 97 Suspected infection = 24 Clotted catheter or thrombosis = 3 Other = 23

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Tennenberg, 1997[59]	Control	TPN = 70 (48%)			Inpatients on the surgical, medical and ICU wards who were deemed by their physicians to require CVC placement for their care. To eliminate the potential contamination associated with CVCs over a guidewire, only patients who required fresh-stick CVC insertion in the subclavian, jugular or femoral sites were eligible	CVC in place for <48 hours, incomplete culture data and CVC placed during an episode of known septicaemia	Catheter site inflammation, catheter site colonisation, CRI, catheter-related septicaemia		70%	Double = 100 Triple = 45	Blood was taken from CVC then wiped with alcohol and removed onto a sterile field	Clinical
	Treatment	TPN = 56 (41%)								Double = 90 Triple = 47		

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Trerotola, 1998[60]	Control	Haemodialysis		End-stage renal failure[a]	All patients referred to section for a tunnelled haemodialysis catheter	Presence of active infection Lack of right internal jugular vein access Inability to sign the consent form Allergy to contrast material or silver Uncorrectable coagulopathy	Catheter infection	Thrombosis rates, CVC stenosis and thrombosis	80%	2		Poor flow = 6 Infection = 6 Fever = 1 Catheter fell out = 1 Cutaneous reaction to the catheter = 0 Hole in the catheter = 0 Return to CAPD = 3 Recovery of renal function = 2 Mature dialysis access graft or fistula = 20 Patient died = 3 Still in place at end of study = 2
	Treatment											Poor flow = 9 Infection = 5 Fever = 0 Catheter fell out = 2 Cutaneous reaction to the catheter = 2 Hole in the catheter = 1 Return to CAPD = 8 Recovery of renal function = 1 Mature dialysis access graft or fistula = 15 Patient died = 4 Still in place at end of study = 2

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Bach, 1999[61]				Cardiac surgery	Patients after cardiac surgery who required a double lumen CVC		Catheter colonisation, catheter-related bacteraemia		80%	2	Swab taken from inner site of hub and insertion site (3-cm diameter), thorough disinfection of the site and removed aseptically	
Boswald, 1999[66]	Control		ABI = 35.4%	Diabetes mellitus = 6 Malignant tumour = 34 Chronic disease = 31	All hospitalised patients who required a non-tunnelled percutaneous catheter with 1, 2, 3 or 4 lumens for >4 days	Pregnant women Body weight <30 kg	Colonisation of catheter, catheter-associated infection			1, 2, 3 or 4	Sterile conditions	End of therapy = 59 Systemic infection = 10 Local infection = 5 Others = 12
	Treatment		ABI = 40.1%	Diabetes mellitus = 8 Malignant tumour = 46 Chronic disease = 35								End of therapy = 55 Systemic infection = 15 Local infection = 3 Others = 6
Collin, 1999[62]	Control	TPN = 19 (31.1%)		Trauma = 70.5% Surgery = 29.5%								
	Treatment	TPN = 21 (41.4%)		Trauma = 56.9% Surgery = 43.1%								

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Darouiche, 1999[70]	Control		Receiving systemic antibiotics = 90%	Cancer = 26% Cardiopulmonary disease = 34% Neurological disorder = 19% Other = 21%	Hospitalised adults at high risk of CVC-related infection and were likely to require a CVC for ⩾3 days	Pregnant women History of allergy to the anti-infective agents	Catheter colonisation	CRBSI, molecular typing, antimicrobial susceptibility	80%	3	Aseptically	No longer needed = 69% Suspected CVC infection = 13% Occluded catheter = 1% Other = 17%
	Treatment		Receiving systemic antibiotics = 89%	Cancer = 28% Cardiopulmonary disease = 32% Neurological disorder = 16% Other = 24%								No longer needed = 67% Suspected CVC infection = 14% Occluded catheter = 3% Other = 16%
Hannan, 1999[63]	Control		Similar between the two groups	Included acute renal and respiratory failure, postoperative care and general medical admission	Requiring elective central venous access		Catheter colonisation	Catheter sepsis rates		3	Skin swab taken then cleaned with iodine	SIRS/sepsis = 62 Local sepsis = 10 No longer needed = 81 Patient died = 24
	Treatment											SIRS/sepsis = 77 Local sepsis = 12 No longer needed = 69 Patient died = 16

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Marik, 1999[71]					Consecutive patients requiring new CVC		Colonisation, catheter-related sepsis	Zone of inhibition		3		No longer required or when CVC related sepsis was suspected
Moss, 2000[67]	Control	Clinical management; routine surgical procedures including coronary artery bypass grafting, cardiac or abdominal surgery or solid organ transplant	All patients received prophylactic antibiotics that included a β-lactum (flucloxacillin or a cephalosporin). Metronidazole was also given if the patient underwent an abdominal operation. Antibiotics were given for 2 days for cardiac or abdominal surgery	Cardiac = 28 Hepatobiliary = 47 Gastrointestinal = 23	Patients >18 years who were admitted to the Queen Elizabeth Hospital, Birmingham, UK, and who required a CVC as part of their clinical management	Allergy or sensitivity to benzalkonium chloride	Incidence of microbial colonisation	Local and systemic CRI and adverse events, retained antiseptic activity of the benzalkonium chloride device following removal		3	Cleaned with sterile normal saline followed by CG 2.5% in industrial methylated spirit, which was allowed to dry for 2 minutes Aseptically removed	Made independently of the research team End of treatment = 97 Other = 1
	Treatment			Cardiac = 35 Hepatobiliary = 59 Gastrointestinal = 12								Made independently of the research team End of treatment = 96 Other = 10

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Sheng, 2000[64]	Control	TPN = 6 (5%)	Prior antibiotic usage = 12 (10%)	Recent surgery = 117 (96%) Azotaemia = 29 (24%) Diabetes = 23 (19%)	All adult patients who were not allergic to chlorhexidine, silver or sulfonamides and were scheduled to receive a CVC	Those who had known bacteraemia or fungaemia Episodes within 2 weeks before the CVC insertion Febrile patients (oral temperature >38°C) and patients with sepsis syndrome within 1 week or at the time of catheter insertion	CRI, colonisation			3		Inflammation at the catheter site or local pus accumulation New episode of fever Leukocytosis that no other infection foci could be attributed to Patient died Bacteraemia or fungaemia identified No more need for central venous catheterisation
	Treatment	TPN = 3 (3%)	Prior antibiotic usage = 7 (6%)	Recent surgery = 106 (94%) Azotaemia = 28 (25%) Diabetes = 24 (21%)								

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Jaeger, 2001[68]	Control	Chemotherapy		Acute myelogenous leukaemia = 13 Acute lymphoblastic leukaemia = 2 Chronic lymphocytic leukaemia = 0 Non-Hodgkin's lymphoma = 3 Hodgkin's lymphoma = 1 Multiple myeloma = 0 Lymphoma = 1 Myelodysplastic syndrome = 1 Breast cancer = 1 Testicular cancer = 1 Melanoma = 2	Cancer patients requiring CVCs for chemotherapy application		Catheter-related colonisation and catheter-related bacteraemia			3		End of treatment = 11 Suspicion of infection = 14
	Treatment			Acute myelogenous leukaemia = 11 Acute lymphoblastic leukaemia = 1 Chronic lymphocytic leukaemia = 1 Non-Hodgkin's lymphoma = 7 Hodgkin's lymphoma = 2 Multiple myeloma = 2 Lymphoma = 0 Myelodysplastic syndrome = 0 Breast cancer = 1 Testicular cancer = 0 Melanoma = 0								End of treatment = 10 Suspicion of infection = 15

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Stoiser, 2002[69]	Control		Median antibiotic index = 93 (NS) Time of implantation 20 received antistaphylococcal antibiotic. By time of removal 20 had received antibiotic therapy	Solid tumour = 17 Haematological disorder = 7 Bone-marrow transplant = 1 Organ transplantation = 16 Immunosuppression = 6	Consecutive patients requiring implantation of CVC		Contamination of CVC	Catheter-related infections		3	Swab from the insertion site, site disinfected and catheter removed In sterile conditions	Termination of therapy Catheter dysfunction Suspicion of CRI
	Treatment		Median antibiotic index = 73 (NS) Time of implantation 10 received antistaphylococcal antibiotic. By time of removal 21 had received antibiotic therapy	Solid tumour = 12 Haematological disorder = 10 Bone-marrow transplant = 4 Organ transplantation = 17 Immunosuppression = 6								
Theaker, 2002[65]	Control				Longer stay critically ill patients electively having four-lumen catheters to facilitate management		Catheter colonisation	Catheter-related sepsis		4	Skin swab taken and site cleaned before removal through clean field	Sepsis = 58 Local sepsis = 10 Not needed = 53 Died = 10
	Treatment											Sepsis = 49 Local sepsis = 7 Not needed = 43 Died = 2

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Bong, 2003[16]	Control	Mainly TPN		Necrotising pancreatitis = 18 Enterocutaneous fistula = 12 Bowel obstruction/ileus = 39 Upper gastrointestinal surgery = 11 Abdominal sepsis = 26 Others = 25	All patients who required central venous access over a period >7 days were eligible to participate	Aged <18, had a history of allergy to silver, needed multilumen central venous access or were pregnant	CRBSI, colonisation		80%	1		No longer needed Catheter leak Thrombophlebitis Insertion site infection CRBSI
	Treatment			Necrotising pancreatitis = 18 Enterocutaneous fistula = 17 Bowel obstruction/ileus = 29 Upper gastrointestinal surgery = 15 Abdominal sepsis = 19 Others = 23								
Chatzinikolaou, 2003[15]	Control	Haemodialysis, acute renal failure		Leukaemia = 29 Lymphoma/myeloma = 15 Solid tumour = 20	Hospitalised adult cancer patients who required haemodialysis through a CVC for >3 days and up to 1 month	Patients who required an exchange of the catheter over guidewire, rather than a new insertion, and those allergic to rifampin and tetracyclines	CRI	Colonisation	80%	2	Aseptic	No longer needed CRI Catheter occlusion
	Treatment			Leukaemia = 33 Lymphoma/myeloma = 15 Solid tumour = 18								

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Corral, 2003[14]	Control				All patients requiring non-tunnelled insertion of a triple-lumen CVC for ⩾4 days	Inserted outside the ICU Remained in place <4 days Dates of insertion and removal were not recorded	Microbial colonisation and CRBSI			3	Following the same methodology as catheter insertion	Discharge from the ICU = 59 Suspected local infection at the catheter site or sepsis = 44
	Treatment											Discharge from the ICU = 74 Suspected local infection at the catheter site or sepsis = 29
Ranucci, 2003[17]	Control		77	Surgical Cardiac = 73 Thoracic non-cardiac = 6 Vascular abdominal = 27 General abdominal = 47 Medical cancer = 4 Cardiovascular = 33 Pulmonary = 40 Neurological = 37 Others = 10	Undergoing a CVC insertion likely to require an indwelling period of ⩾3 days for either medical or surgical pathologies		Catheter colonisation	CRBSI	80%	2	Aseptically	No longer needed = 209 Suspected catheter infection = 36 Occluded catheter = 5 Others = 27
	Treatment		71	Surgical Cardiac = 73 Thoracic non-cardiac = 7 Vascular abdominal = 24 General abdominal = 51 Medical cancer = 7 Cardiovascular = 22 Pulmonary = 37 Neurological = 37 Others = 10								No longer needed = 210 Suspected catheter infection = 36 Occluded catheter = 2 Others = 20

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Brun-Buisson, 2004[13]	Control	Medical = 68 Surgical scheduled = 23 Surgical emergency = 48 Non-operative trauma = 36	At inclusion = 115	Severity None or non-fatal = 115 Ultimately fatal = 53 Rapidly fatal = 7	When insertion of a CVC at a new site (subclavian or internal jugular) was planned for therapy or monitoring of ⩾3-day duration		CVC-related infection, including catheter-related bacteraemia and non-bacteraemia, catheter-related sepsis	Incidence of CVC-related bloodstream infection and of catheter colonisation	80%	Single = 31 Double = 144		No longer required Malfunction Suspicion of infection Unexplained BSI Presence of gross inflammation or pus at the catheter insertion site
	Treatment	Medical = 88 Surgical scheduled = 19 Surgical emergency = 51 Non-operative trauma = 33	At inclusion = 111	Severity None or non-fatal = 128 Ultimately fatal = 55 Rapidly fatal = 8						Single = 35 Double = 156		
Carrasco, 2004[12]	Control	TPN = 26	107	Medical = 50 Surgical = 23 Traumatic = 18	Admitted to ICU in need of a triple-lumen CVC		Catheter colonisation, CRBSI			3	Aseptically	
	Treatment	TPN = 24	109	Medical = 55 Surgical = 21 Traumatic = 13								

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Hanna, 2004[11]	Control	Chemotherapy, bone-marrow transplantation	Receiving prophylactic antibiotics at catheter insertion = 37 Received systemic antibiotic during study = 71	Leukaemia = 19 Melanoma = 23 Multiple myeloma = 3 Lymphoma = 40 Sarcoma = 25 Solid tumour = 64	Adult patients with cancer who required new insertion of a non-tunnelled peripherally inserted CVC (PICC) or subclavian catheter (single or double lumen) with use anticipated to be >7 days and who were available to be followed for up to 100 days	Patients who were allergic to rifampin or tetracyclines, as well as pregnant women	CRBSI		80%	1 or 2 subclavian 1 PICC		Catheter no longer needed = 100 Mechanical problem = 3 Suspected infection = 19 Other = 18
	Treatment		Receiving prophylactic antibiotics at catheter insertion = 25 Received systemic antibiotic during study = 61	Leukaemia = 12 Melanoma = 33 Multiple myeloma = 6 Lymphoma = 44 Sarcoma = 26 Solid tumour = 70								Catheter no longer needed = 127 Mechanical problem = 4 Suspected infection = 9 Other = 14

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Leon, 2004[10]	Control			Surgical = 52 Trauma = 21 Medical = 107	Consecutive patients >17 years, admitted to ICUs, likely to need a CVC at a new insertion site for >3 days	Allergy to minocycline or rifampin	Colonisation	CRBSI and catheter-related clinical infectious complications	80%	3	Aseptically	No longer needed = 67 Suspected catheter infection = 490 Planned line replacement = 26 Inflammation at insertion site = 15 Occluded catheter = 6 Death = 15
	Treatment			Surgical = 54 Trauma = 23 Medical = 110								No longer needed = 81 Suspected catheter infection = 39 Planned line replacement = 20 Inflammation at insertion site = 9 Occluded catheter = 4 Death = 27

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Yücel, 200[49]	Control			Cancer = 41 Heart/vascular surgery = 23 Peripheral vascular surgery = 15 Gastroenterology = 13 Traumatology = 10 Urology = 2 Plastic surgery = 1 Neurology = 0	Hospitalised adults (18–80 years) assumed to require a CVC for ⩾3 days and undergoing first central venous catheterisation	Pregnancy, known allergy to miconazole and/or rifampicin, anatomical defect or skin lesions at the potential site of insertion, and previous inclusion in the present trial	Colonisation, cather-related infections		80%	3	By a study nurse or the physician in charge of this study. The catheter was carefully removed with the outside portion pointing upwards to reduce potential contamination by micro-organisms on the skin surface	Regular termination of catheterisation = 87 Preterm removal of CVC = 18 Reasons for preterm removal Redness and/or pain at the site of insertion = 5 Fever or suspected infection = 8 Technical problems = 4 Death = 1
	Treatment			Cancer = 43 Heart/vascular surgery = 33 Peripheral vascular surgery = 17 Gastroenterology = 15 Trauma = 5 Urology = 2 Plastic surgery = 1 Neurology = 2								Regular termination of catheterisation = 104 Preterm removal of CVC = 14 Reasons for preterm removal Redness and/or pain at the site of insertion = 4 Fever or suspected infection = 5 Technical problems = 4 Death = 1

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Jaeger, 2005[8]	Control	Chemotherapy	No sig. difference	Acute myelogenous leukaemia = 39 Acute lymphoblastic leukaemia = 5 Chronic lymphoblastic leukaemia = 2 Non-Hodgkin's lymphoma = 6 Multiple myeloma = 3	Consecutive leukaemic patients requiring CVC for chemotherapy application		Catheter-related colonisation, catheter-related bacteraemia		80%	3		End of treatment = 22 Suspicion of infection = 33
	Treatment			Acute myelogenous leukaemia = 34 Acute lymphoblastic leukaemia = 7 Chronic lymphoblastic leukemia = 2 Non-Hodgkin's lymphoma = 4 Multiple myeloma = 4								End of treatment = 21 Suspicion of infection = 28

continued

TABLE 41 *Study characteristics (cont'd)*

Study	Group	Reason for CVC	Antibiotic usage	Illness	Inclusion criteria	Exclusion criteria	Primary outcome	Secondary outcomes	Power calculation	Lumens	Removal technique	Reason for removal
Rupp, 2005[18]	Control	TPN = 124	359	Cardiovascular = 70 Neurological = 28 Respiratory = 151 Gastrointestinal = 75 Renal = 12 Metabolic = 4 Haematological = 10 Other = 12	Adult, critical care units, triple-lumen CVC access	Pregnant Allergic to chlorhexidine or sulfa drugs Hospitalised for burn injuries Chronic inflammatory skin disorder Suspected of having a catheter Associated infection or were enrolled in another investigational trial	Effectiveness of second generation antiseptic-coated catheter in the prevention of microbial colonisation and infection	Safety and tolerability of this device Microbiology of infected catheters Propensity for the development of antiseptic resistance	80%	3	Aseptically	No longer needed = 219 Death = 28 Suspected infection with local signs = 26 Suspected infection without local signs = 57 Occlusion or thrombosis = 9 Malfunction = 3 Other = 54
	Treatment	TPN = 131	353	Cardiovascular = 58 Neurological = 16 Respiratory = 132 Gastrointestinal = 103 Renal = 17 Metabolic = 3 Haematological = 6 Other = 10								No longer needed = 193 Death = 35 Suspected infection with local signs = 25 Suspected infection without local signs = 44 Occlusion or thrombosis = 10 Malfunction = 6 Other = 64

[a] Information from correspondence with authors.

ABI, Antibiotic index (No. of days of antimicrobial therapy : No. of days of catheter insertion); CAPD, continuous ambulatory peritoneal dialysis; FAS, fibrin analysis system; SIRS, systemic inflammatory response syndrome.

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No. 12
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We look forward to hearing from you.

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