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The research reported in this monograph was commissioned by the HTA Programme as project number 05/29/01. The contractual start date was in September 2005. The draft report began editorial review in May 2006 and was accepted for publication in February 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

Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections

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Objectives: To determine the clinical effectiveness and cost-effectiveness of (1) alternative strategies for the prevention of *Staphylococcus aureus* carriage in patients on peritoneal dialysis (PD) and (2) alternative strategies for the eradication of *S. aureus* carriage in patients on PD.
Data sources: Major electronic databases were searched up to December 2005 (MEDLINE Extra up to 6 January 2006).
Review methods: Electronic searches were undertaken to identify published and unpublished reports of randomised controlled trials and systematic reviews evaluating the effectiveness of preventing and treating *S. aureus* carriage on peritoneal catheter-related infections. The quality of the included studies was assessed and data synthesised. Where data were not sufficient for formal meta-analysis, a qualitative narrative review looking for consistency between studies was performed.
Results: Twenty-two relevant trials were found. These fell into several groups: the first split is between prophylactic trials, aiming to prevent carriage, and trials which aimed to eradicate carriage in those who already had it; the second split is between antiseptics and antibiotics; and the third split is between those that included patients having the catheter inserted before dialysis started and people already on dialysis. Many of the trials were small or short-term. The quality was often not good by today's standards. The body of evidence suggested a reduction in exit-site infections, but this did not seem to lead to a significant reduction in peritonitis, although to some extent this reflected insufficient power in the studies and a low incidence of peritonitis in them. The costs of interventions to prevent or treat *S. aureus* carriage are relatively modest. For example, the annual cost of antibiotic treatment of *S. aureus* carriage per identified carrier of *S. aureus* was estimated at £179 (£73 screening and £106 cost of antibiotic). However, without better data on the effectiveness of the interventions, it is not clear whether such costs are offset by the cost of treating infections and averting changes from peritoneal dialysis to haemodialysis. Although treatment is not expensive, the lack of convincing evidence of clinical effectiveness made cost-effectiveness analysis unrewarding at present. However, consideration was given to the factors needed in a hypothetical model describing patient pathways from methods to prevent *S. aureus* carriage, its detection and treatment and the detection and treatment of the consequences of *S. aureus* (e.g. catheter infections and peritonitis). Had data been available, the model would have compared the cost-effectiveness of alternative interventions from the perspective of the UK NHS, but as such it helped identify what future research would be needed to fill the gaps.
Conclusions: The importance of peritonitis is not in doubt. It is the main cause of people having to switch from peritoneal dialysis to haemodialysis, which then leads to reduced quality of life for patients

and increased costs to the NHS. Unfortunately, the present evidence base for the prevention of peritonitis is disappointing; it suggests that the interventions reduce exit-site infections, but not peritonitis, although this may be due to trials being in too small numbers for too short periods. Trials are needed with larger numbers of patients for longer durations.

Contents

List of abbreviations

CEAC	cost-effectiveness acceptability curve
CI	confidence interval
EPO	erythropoietin
EURODICE	European Dialysis and Cost Effectiveness
HCHS	Hospital and Community Health Services
HD	haemodialysis
ITT	intention-to-treat
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *Staphylococcus aureus*
NICE	National Institute for Health and Clinical Excellence
PD	peritoneal dialysis
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SA	*Staphylococcus aureus*

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

Objectives

The objectives of this review were to determine the clinical effectiveness and cost-effectiveness of alternative strategies for the prevention and eradication of *Staphylococcus aureus* carriage in patients on peritoneal dialysis (PD). The aim was to prevent, or reduce, the frequency of peritonitis. The review does not cover treatment of peritonitis itself.

Background and intervention

In chronic renal failure, dialysis is used to replace the kidneys' function in removing impurities and unwanted products of metabolism from the blood. Peritoneal dialysis is a form of ambulatory dialysis in which fluid is fed into the abdominal cavity via a catheter through the abdominal wall. The fluid collects the substances normally excreted by the kidney. After an interval the fluid is drained out again.

The main complication of peritoneal dialysis in the short term is infection of the peritoneal cavity, peritonitis. In the longer term, recurrent episodes of peritonitis can impair diffusion across the peritoneal membrane, so that peritoneal dialysis is no longer feasible, which means that patients have to attend hospital for haemodialysis, usually three times per week.

One of the organisms which cause peritonitis is *Staphylococcus aureus*. It can colonise parts of the body without symptoms, but may cause infection where the peritoneal catheter passes through the skin of the abdomen. These are known as exit-site infections. It may also contaminate the tip of the catheter. In both situations, peritonitis may be a consequence.

Various measures have been used to try to prevent or eradicate colonisation, in the hope that this will prevent, or reduce, the frequency of peritonitis. These include antiseptics and antibiotics. The antibiotics can be applied locally or given systemically, by mouth.

S. aureus can develop resistance to commonly used antibiotics, and is then known as methicillin-resistant *Staphylococcus aureus* (MRSA).

Epidemiology

End-stage renal failure can be a consequence of a number of diseases, the commonest being glomerulonephritis, diabetes, renal vascular disease, pyelonephritis and polycystic kidney disease.

Methods

Electronic searches were undertaken to identify published and unpublished reports of randomised controlled trials (RCTs) and systematic reviews evaluating the effectiveness of preventing and treating *S. aureus* carriage on peritoneal catheter-related infections. The main databases searched were MEDLINE (1966–2005), EMBASE (1980–2005), CINAHL (1982–2005), BIOSIS (1985–2005), Science Citation Index (SCI) (1980–2005), MEDLINE Extra (6 January 2006), Cochrane Library (Issue 4 2005), Database of Abstracts of Reviews of Effectiveness (December 2005) and HTA Database (December 2005). The quality of the included studies was assessed and data synthesised. Where data were not sufficient for formal meta-analysis, a qualitative narrative review looking for consistency between studies was performed.

Results

Number and quality of studies and summary of benefits

Twenty-two trials were found. These fell into several groups: the first split is between prophylactic trials, aiming to prevent carriage, and trials which aimed to eradicate carriage in those who already had it; the second split is between antiseptics and antibiotics; and the third split is between those that included patients having the catheter inserted before dialysis started and people already on dialysis. Many of the trials were small or short-term. The quality was often not good by today's standards. The body of evidence suggested a reduction in exit-site infections but this did not seem to lead to a significant reduction in peritonitis, although to some extent this reflected insufficient power in the studies and a low incidence of peritonitis in them.

Costs

The costs of interventions to prevent or treat *S. aureus* carriage are relatively modest. For example, the annual cost of antibiotic treatment of *S. aureus* carriage per identified carrier of *S. aureus* was estimated at £179 (£73 screening and £106 cost of antibiotic). However, without better data on the effectiveness of the interventions, it is not clear whether such costs are offset by the cost of treating infections and averting changes from peritoneal dialysis to haemodialysis.

Cost-effectiveness

Although treatment is not expensive, the lack of convincing evidence of clinical effectiveness made cost-effectiveness analysis unrewarding at present. However, consideration was given to the factors needed in a hypothetical model describing patient pathways from methods to prevent *S. aureus* carriage, its detection and treatment and the detection and treatment of the consequences of *S. aureus* (e.g. catheter infections and peritonitis). Had data been available, the model would have compared the cost-effectiveness of alternative interventions from the perspective of the UK NHS, but as such it helped identify what future research would be needed to fill the gaps.

Conclusions

The importance of peritonitis is not in doubt. It is the main cause of people having to switch from peritoneal dialysis to haemodialysis, which leads to reduced quality of life for patients and increased costs to the NHS. Unfortunately, the present evidence base for the prevention of peritonitis is disappointing; it suggests that the interventions reduce exit-site infections but not peritonitis, although this may be due to trials being in too small numbers for too short periods.

Recommendations for research

The study identified key research questions that need to be addressed. These are given below.

- What is the natural history of carriage of *S. aureus*? What are the links between carriage and exit-site infection, and between exit-site infection and peritonitis? What factors predict carriage?
- Is the problem mainly with MRSA, with methicillin-sensitive *Staphylococcus aureus* (MSSA) being relatively harmless?
- Does decolonisation work, or is recolonisation rapid?
- Apart from antibiotic and antiseptic use, what other options for reducing peritonitis are there? Would more training help?
- Should measures to eradicate carriage be intermittent or chronic; antiseptics versus antibiotics?
- Is vaccination worth revisiting?
- Given the common use of mupirocin in renal units, research into that drug and resistance to it should be a priority.

Trials are needed with larger numbers of patients for longer durations.

Chapter 1

Objectives of the review

The objectives of this review were to determine the clinical effectiveness and cost-effectiveness of alternative strategies for the prevention and eradication of *Staphylococcus aureus* carriage in patients on peritoneal dialysis (PD). The aim was to prevent, or reduce, the frequency of peritonitis. The review does not cover treatment of peritonitis itself.

Chapter 2
Background

Description of the problem

S. aureus is a bacterium that lives completely harmlessly on the skin and in the nose of about one-third of normal healthy people. This situation can be called colonisation or carriage. Other *S. aureus* carriage sites include the axillae, vagina, perineum and occasionally the gastrointestinal tract.

However, although colonisation of those sites may not cause any problems there, the presence of the organism means that more vulnerable parts of the body may be first contaminated and then infected. In PD, a catheter is inserted into the abdominal cavity though the skin of the abdominal wall and exits through a subcutaneous tunnel. Whenever the skin is broken, there is a risk of infection. Hence people on PD are at increased risk because of the break in the skin. Some may also be at increased risk of all infections because of the diseases which lead to renal failure, such as diabetes.

PD is used more in the UK than in other countries. Almost one-third of the dialysis population in the UK are on PD[1] and 50% of PD patients are known to be *S. aureus* carriers.[2] Some studies have reported that nasal carriage of *S. aureus* is more frequent in diabetic and immunosuppressed PD patients.[3,4]

PD catheter-related infections are an important cause of morbidity and mortality in the PD population. Such infections are classified into exit-site, tunnel infections and peritonitis. An exit-site infection is defined as purulent drainage at the catheter exit site with or without erythema. A tunnel infection is an infection of the tissues overlying the subcutaneous portion of the catheter.[5] Peritonitis is inflammation of the peritoneal membrane. Exit-site or tunnel infections cause significant morbidity as they can lead to refractory or recurrent peritonitis.[6] Peritonitis is associated with several adverse consequences. It accounts for the majority of occasions when the PD catheter has to be removed, leading to transfer to haemodialysis (HD).[7,8] Peritonitis is one of the most common causes for hospitalisation in PD patients.[9] It contributes to the decline of peritoneal membrane function, which means that PD may become impossible. It may also lead to a more rapid decline in residual renal function (i.e. some patients still have a little function left in their kidneys) and is an important predictor of survival.[10]

Although there can be many different causes of PD catheter-related infections, *S. aureus* is an important cause. It is believed to be the leading cause of PD catheter exit-site infection[11,12] and one of the most frequent causes of PD-related peritonitis.[13] It has been estimated that the peritonitis rates due to *S. aureus* are 0.09–0.22 per dialysis year.[2,14] The cost of *S. aureus* infections in the dialysis population in the USA has been estimated to be over US$200 million annually.[15]

Several studies have shown a strong link between *S. aureus* carriage and PD catheter exit-site and tunnel infections[16–18] and peritonitis.[19,20] *S. aureus* carriers, have a two- to six-fold higher risk of *S. aureus* peritonitis than non-carriers.[2,19]

Peritonitis due to *S. aureus* tends to be more severe than that due to other organisms, with patients more likely to have fever and hypotension.[21] Hospital admission may be prolonged with *S. aureus* peritonitis[9] and it also increases mortality.[22,23] Furthermore, removal of the PD catheter is required more often in *S. aureus* peritonitis than with peritonitis due to other bacteria, to resolve the peritonitis or prevent recurrence.[24] Removal of the catheter means that PD has to be replaced by HD, requiring at least temporary attendance at hospital dialysis sessions, usually three times per week.

Descriptions of interventions

Studies comparing carriage and infecting *S. aureus* isolates have shown that patients are infected with their 'own' organism, that is, the one they carry on skin or nose.[2,25,26] Although *S. aureus* is found in the body in areas other than the nose, elimination of nasal carriage also leads to loss of carriage in other sites such as hands and skin,[27] implying that the other parts are being reinfected from the nose. In addition, the PD catheter exit site is reported to be most important colonising site of *S. aureus*

strains that cause peritonitis.[28] These important observations underpin strategies that aim to reduce *S. aureus*-related PD catheter infections and peritonitis.

S. aureus is normally susceptible to a variety of antibiotics, the most commonly used of which is mupirocin, given as an ointment.

Recommendations according to various guidelines

Various bodies have made recommendations, although these are not necessarily followed in practice.

- Renal Association (UK):[29] Peritonitis rates should be less than one episode per 18 patient months. Mupirocin should be applied to the exit site either daily or on alternate days. Nasal carriage of *S. aureus* should be treated with mupirocin twice daily for five consecutive days every 4 weeks.
- European Renal Association–European Dialysis and Transplantation Association (ERA–EDTA):[30] Mupirocin should be applied either at the exit site or intranasally especially in patients who are *S. aureus* carriers.
- International Society of Peritoneal Dialysis:[31] Several options are recommended: exit-site mupirocin daily in all patients or in *S. aureus* carriers only or in response to positive *S. aureus* culture; intranasal mupirocin every month in those identified as carriers or only in response to positive nose culture; exit-site gentamicin in all patients.
- Caring for Australians with Renal Impairment (CARI guidelines):[32–34] Prophylactic therapy using mupirocin ointment, especially for *S. aureus* carriage intranasally, is recommended to decrease the risk of *S. aureus* catheter exit site/tunnel infections and peritonitis.

It is clear that although all guidelines recommend mupirocin for *S. aureus* nasal carriers, there is considerable variation with other recommendations. There has been no systematic review of evidence for the effectiveness of interventions for prevention and treatment of *S. aureus* carriage in PD patients. It was against this background that the NHS Research and Development Programme for Health Technology Assessment (HTA) commissioned this study.

Chapter 3

Efficacy and safety

Methods for reviewing effectiveness

Search strategy

Electronic searches were undertaken to identify published and unpublished reports of randomised controlled trials (RCTs) and systematic reviews evaluating the effectiveness of preventing and treating *S. aureus* carriage on peritoneal catheter-related infections.

The main databases searched were MEDLINE (1966–2005), EMBASE (1980–2005), CINAHL (1982–2005), BIOSIS (1985–2005), Science Citation Index (SCI) (1980–2005), MEDLINE Extra (6 January 2006), Cochrane Library (Issue 4 2005), Database of Abstracts of Reviews of Effectiveness (December 2005) and HTA Database (December 2005). Searching was restricted to English language publications only. In addition, recent conference proceedings, tables of contents of two key PD journals and reference lists of all included studies were scanned to identify additional potentially relevant studies. Full details of the search strategies used are documented in Appendix 1.

All titles and abstracts identified in these ways were assessed to identify potentially eligible studies. Two reviewers independently assessed them for inclusion, using a study eligibility form developed for this purpose (Appendix 2). Any disagreements were resolved by consensus or arbitration. Systematic reviews were used to identify RCTs but were not otherwise included in this review.

Inclusion and exclusion criteria

Types of studies

All published RCTs and quasi-RCTs (e.g. allocation by alternation) of patients receiving PD for end-stage renal disease in whom alternative interventions were compared for the prevention and treatment of *S. aureus* carriage were included. For the purposes of this review, studies comparing alternative interventions for the treatment of clinical infections and studies which did not report outcomes separately for *S. aureus* were excluded.

Types of participants

The trials included patients on PD for end-stage renal disease from any cause.

Types of outcomes

The following measures of outcomes were sought:

Primary outcome:

1. number of patients with peritonitis caused by *S. aureus*.

Secondary outcomes:

1. number of patients with *S. aureus* carriage
2. time to *S. aureus* carriage
3. peritonitis rate (number of episodes over total patient months on PD) caused by *S. aureus*
4. time to first peritonitis episode caused by *S. aureus*
5. peritonitis relapse (number and specify time to) caused by *S. aureus*
6. number of patients requiring catheter removal caused by *S. aureus*
7. number of patients switching to HD caused by *S. aureus*
8. number of patients requiring catheter replacement caused by *S. aureus*
9. number of patients with exit-site and/or tunnel infections caused by *S. aureus*
10. exit-site and/or tunnel infection rate caused by *S. aureus*
11. side-effects
12. death due to peritonitis caused by *S. aureus*
13. hospitalisation rates
14. quality of life
15. development of antibiotic resistance.

Data extraction strategy

The titles and abstracts of all papers identified by the search strategy were screened. Full text copies of all potentially relevant studies were obtained and assessed for inclusion. Reviewers were not blinded to the names of studies' authors, institutions or sources of the reports. Any disagreements were resolved by consensus or arbitration.

A data extraction form was developed to record details of trial methods, participants, interventions, patient characteristics and outcomes (Appendix 3).

Two reviewers independently extracted data from the included studies. Any differences that could not be resolved through discussion were referred to an arbiter.

Quality assessment strategy

Two reviewers, working independently, assessed the methodological quality of the included studies. Again, any disagreements were resolved by consensus or arbitration. The system for classifying methodological quality of controlled trials was based on an assessment of four principal potential sources of bias: selection bias caused by inadequate concealment of allocation of treatments; attrition bias caused by losses to follow-up without appropriate intention-to-treat (ITT) analysis; detection bias caused by biased ascertainment of outcome where knowledge of the allocation might have influenced the measurement of outcome; and selection bias in analysis (Appendix 3).

Data synthesis

For trials with multiple publications, only the most up-to-date data for each outcome were included. Dichotomous outcome data were combined using the Mantel–Haenszel relative risk (RR) method and 95% confidence intervals (CIs) and *p*-values were calculated for the estimates. The results were all reported using a fixed-effects model. χ^2 tests and I^2 statistics were used to explore statistical heterogeneity across studies and, when present, random effects methods were applied. Other possible reasons for heterogeneity were explored using sensitivity analyses. The meta-analyses were conducted using the standard Cochrane software RevMan 4.2.

Where data were not sufficient for formal meta-analysis, a qualitative narrative review looking for consistency between studies was performed.

Results

Quantity and quality of research available

Number of studies identified

The results of the searches are summarised in *Table 1*. The numbers retrieved from the searches in CINAHL, SCI, Biosis and CENTRAL and screening of full text journals include only the additional reports found after excluding those identified from the MEDLINE/EMBASE multifile search.

A total of 498 titles and abstracts were identified from the various searches, of which 394 were clearly outwith the scope of this review. The remaining 104 reports (90 full text papers and 14 abstracts) were selected for full assessment. *Table 2* details the numbers of these that were included and excluded.

TABLE 1 *Search results*

Database	No. retrieved
MEDLINE/EMBASE/MEDLINE Extra multifile search (after deduplication in Ovid)	381
CINAHL	23
SCI	56
BIOSIS	12
CENTRAL	2
CDSR	1
DARE	7
HTA database	2
NRR	1
CCT	0
Clinical Trials	0
SCI Proceedings	2
Selected from conference abstracts	2
Selected from full text journals	9
Total	**498**

TABLE 2 *Papers selected for full assessment*

Assessment	No. of papers
Included in review	25
Systematic reviews	7
Retained for background information	26
Excluded – not RCTs	17
Excluded – treatment of clinical infections	7
Excluded – outcomes not reported separately for *S. aureus* carriage	22
Unobtainable papers	0
Total	**104**

Number and type of studies included

Twenty-five reports (21 full text papers and four abstracts) describing 22 RCTs met the inclusion criteria for the review and were included in the review of clinical effectiveness. The majority of these reports were identified from the MEDLINE/EMBASE search (20), with two each identified from SCI and the full text journals and one from BIOSIS. The list of included studies and associated references are listed in Appendix 4. No studies were identified only from CINAHL.

Trials fell into several groups. The first split is between prophylactic trials, aiming to prevent

carriage, and between trials which aimed to eradicate carriage in those who already had it. The second split is between antiseptics and antibiotics. The third split is between those that included patients having the catheter inserted before dialysis started and those where the people were already on dialysis.

Number and type of studies excluded, with reasons for specific exclusions

A total of 46 reports were obtained but subsequently were excluded because they failed to meet one or more of the inclusion criterion. Of these, 17 were not RCTs, seven were concerning the treatment of clinical infections and in 22 the authors did not report outcomes separately for participants with *S. aureus* carriage (18 primary reports and four secondary reports).

Study quality, characteristics and evidence rating

A summary of the quality assessment of the 22 RCTs is presented in *Table 3* and the detailed quality assessment for each of the included studies is reported in Appendix 5. The method of randomisation used was stated explicitly for 11 of 22 trials: a central randomisation service was used in one study, consecutively numbered, sealed envelopes were used in one study, computer-generated random numbers were used in one study, there was consecutive allocation in two, by random numbers table in three, by date of follow-up in one, assigned by a third party in one and random selection by cards in one. By modern standards, most of these methods are unsatisfactory, but some of the trials were done some time ago. In 11 trials, the allocation was said to be 'randomised' but the method was not specified. Concealment of allocation was adequate in only one trial, suboptimal in four and unclear in 17.

In the majority of trials, it was unclear whether studies blinded the care provider, participant, outcome assessor or data analyst (but it is questionable if this is possible given the nature of the treatments compared). Five studies included an ITT analysis but it was unclear if this were the case for the remaining 25 studies.

Eligibility criteria were clearly specified in 21 studies. The mean or median duration of follow-up ranged from at least 48 hours to 1 year. This was not reported for three studies.

Characteristics of included studies

The comparisons made and characteristics of the RCTs are summarised in *Table 4* and a detailed description for each of the included studies is reported in Appendix 6. Within the 22 eligible RCTs, there were 30 relevant comparisons (four trials had three arms). Three trials took place in the UK, eight in the USA, two in Hong Kong, two in Brazil and one each in Spain, Turkey, Singapore and Canada. There were two multi-centre European trials and one multi-centre Australia and New Zealand trial. Across the trials recruitment dates ranged from May 1987 to August 2003. Eleven trials failed to provide information on recruitment dates. The number of participants randomised ranged from 15 to 267. Two trials had more than 200 participants, eight more than 100 participants and 12 fewer than 100 participants. Eighteen trials gave details of the numbers of men and women in each trial group. Seventeen trials gave details of participants' ages. One trial included children only.

Assessment of effectiveness

Table 5 gives a summary of the outcomes reported in the included studies.

Prophylaxis amongst all patients

Eighteen trials evaluated prophylaxis amongst all patients regardless of their *S. aureus* status at trial entry. Four trials evaluated prophylaxis at the time of catheter insertion and the remaining trials considered prophylaxis given once dialysis had commenced. Five trials compared antibiotic treatment with no antibiotic treatment, four trials compared two different antibiotic regimes, one three-armed trial compared two different antibiotic regimes with no antibiotic treatment, three trials compared antiseptic treatment with no antiseptic treatment, one trial compared two different types of antiseptics, one trial compared a vaccination with combined staphylococcus

TABLE 3 *Summary of the quality assessment of the included RCTs*

Allocation concealment	Blinding of investigators	Blinding of participants	Blinding of assessor	Blinding of data analysis	ITT	Lost to follow-up
Adequate: 1 Inadequate: 4 Unclear: 17	Yes: 1 No: 5 Unclear: 17	Yes: 2 No: 4 Unclear: 16	Yes: 1 No: 2 Unclear: 19	Yes: 0 No: 1 Unclear: 21	Stated: 3 Not stated: 19	Yes: 12 No: 0 Unclear: 10

TABLE 4 *Summary of the comparisons made and baseline characteristics*

Study	Comparison	No. of participants	Age (years)[a]	Male/female
Prophylaxis amongst all patients				
Antibiotic versus no antibiotic				
Catheter insertion:				
Bennett-Jones, 1988[35]	I.v. gentamicin	13	52.7 ± 18.6[b]	8/5
	No treatment	13	52.7 ± 18.6[b]	9/4
Lye, 1992[36]	I.v. cefazolin and gentamicin	25	56.0 ± 14.3	8/17
	No treatment	25	52.3 ± 14.0	15/10
During dialysis:				
Sharma, 1971[37]	Neomycin by mouth or nasogastric tube	48 dialysates	–	–
	Placebo	41 dialysates	–	–
Wong, 2003[38]	Mupirocin ointment	78 (73 analysed)	60 ± 12[c]	32/41
	No treatment	88 (81 analysed)	59 ± 13[c]	47/34
Zimmerman, 1991[39]	Rifampin	32	53 ± 3	17/15
	No treatment	32	55 ± 4	24/8
Antibiotic versus antibiotic				
During dialysis:				
Bernardini, 1996[40]	Mupirocin ointment	41	–	49%/51%
	Oral rifampin	41	–	59%/41%
Bernardini, 2005[41,42]	Mupirocin ointment	66	51 ± 15	38/28
	Gentamicin ointment	67	51 ± 15	34/33
Cavdar, 2004[43]	Mupirocin ointment applied once weekly	18	55.3 ± 1.8[c]	10/8
	Mupirocin ointment applied thrice weekly	18	55.0 ± 2.3[c]	11/7
Antibiotic versus antibiotic versus no antibiotic				
Catheter insertion:				
Gadallah, 2000[44,45]	I.v. vancomycin	90 (103 procedures)	46 (15 to 72)[b]	38/52
	I.v. cefazolin	88 (102 procedures)	47 (20 to 81)[b]	43/45
	No treatment	87 (100 procedures)	45 (19 to 76)[b]	38/49
Antiseptic versus no antiseptic				
Catheter insertion:				
Waite, 1997[46]	Povidone–iodine ointment	61	54.4 ± 15.1	33/28
	No treatment	56	53.2 ± 14.5	30/26
During dialysis:				
Luzar, 1990[3]	Povidone–iodine	74	–	63%/37%
	Non-disinfectant soap	53	–	59%/41%
Sesso, 1988[47]	Chlorhexidine	20	–	–
	Neutral soap	19	–	–
Wilson, 1997[48]	Povidone–iodine spray	77 catheters	53 (18–82)[e]	55/22
	No treatment	72 catheters	51 (21–76)[e]	43/29
Wong, 2002[49]	Chlorhexidine liquid soap	69	59.0 ± 11.50[b]	34/35
	Pure liquid soap	48	56.3 ± 11.7[b]	23/25
Antiseptic versus antiseptic				
During dialysis:				
Fuchs, 1990[50]	Chlorhexidine	18	46[c]	7/11
	Sodium hypochlorite	13	47[c]	7/6
	Povidone–iodine swabsticks plus povidone ointment	20	55[c]	13/7
Other				
During dialysis:				
Poole-Warren, 1991[51]	Vaccination	65	54 ± 11	1.5 (ratio)
	Placebo	59	52 ± 14	0.7 (ratio)

continued

TABLE 4 *Summary of the comparisons made and baseline characteristics (cont'd)*

Study	Comparison	No. of participants	Age (years)[a]	Male/female
Turner, 1992[52]	Catheter immobiliser	22	45 ± 15.51	–
	Tape	23	40 ± 14.26	–
	Non-immobilisation	21	43 ± 15.8	–
Warady, 2003[53]	'Flush before fill'	62	11.4 ± 5.6[d]	54.8%/45.2%
	Flushing with 15 ml of sterile dialysate	59	11.2 ± 6.0[d]	59.3%/40.7%
Treatment of *S. aureus* carriage				
Antibiotic versus no antibiotic				
During dialysis:				
Blowey, 1994[54]	Oral rifampin plus bacitracin	7	–	
	No treatment	8	–	
Mupirocin Study Group, 1996[55,56]	Mupirocin ointment	134	60.3[c]	60.4%/39.6%
	Placebo ointment	133	60.3[c]	60.2%/39.8%
Antibiotic versus antibiotic				
During dialysis:				
Perez-Fontan, 1992[57]	Mupirocin nasal ointment	12	51 ± 15[b]	5/7
	Neomycin sulphate ointment	10	48 ± 21[b]	5/5
Antibiotic versus antibiotic versus no antibiotic				
During dialysis:				
Sesso, 1994[58]	Sodium fusidate ointment	9	46.1 ± 3.8 (33–69)[e]	6/3
	Oral ofloxacin	9	36.6 ± 4.6 (22–61)[e]	6/3
	Placebo tablets	13	42.1 ± 4.6 (17–68)[e]	9/4

[a] Data are expressed as mean ± standard deviation (SD) unless stated otherwise.
[b] Measure unclear.
[c] Mean.
[d] Mean ± standard error of the mean (SEM).
[e] Mean ± standard error (range).

toxoid/whole killed staphylococci formulation with a placebo, one three-armed trial compared a catheter immobiliser with the use of tape and non-immobilisation and one trial compared the 'flush before fill' technique with standard practice.

Table 6 provides details, where reported, of the results for the following outcomes: number of patients with *S. aureus* carriage (at trial entry); number of patients with peritonitis; peritonitis rate (number of episodes over total patient months on PD); number of patients requiring catheter removal; number of patients with exit-site and/or tunnel infections; and the exit-site and/or tunnel infection rate.

Time to *S. aureus* carriage

One trial, comparing vaccination with a combined staphylococcus toxoid/whole killed staphylococci formulation (SB) given intramuscularly with placebo,[51] also reported the number of *S. aureus*-positive nasal swabs relative to the total nasal swabs taken at each time point (*Table 7*).

Time to the first peritonitis episode

One trial comparing intravenous vancomycin approximately 12 hours before catheter placement with intravenous cefazolin approximately 3 hours before catheter placement with no antibiotics for at least 1 week before procedure, reported the time to the first peritonitis episode.[44] There was one case of peritonitis at 6 days in the intravenous cefazolin and two cases of peritonitis at 1 and 4 days in the group allocated to receive no antibiotics at least 1 week before surgery.

Side-effects

Three trials reported side-effects of antibiotic prophylaxis: Bernardini and colleagues[40] reported that four out of 41 patients experienced nausea and vomiting in the oral rifampin group and one other required liver function tests. There were no reported side-effects in the mupirocin group. Bernardini and colleagues[41] reported exit-site irritation in seven out of 66 patients in the mupirocin group and seven out of 67 patients in the gentamicin group. Wilson and colleagues[48]

TABLE 5 *Summary of outcomes reported in the included studies*

Study ID	Outcomes														
	No. of patients with *S. aureus* carriage	Time to *S. aureus* carriage	No. of patients with peritonitis	Peritonitis rate	Time to first peritonitis episode	Peritonitis relapse	No. of patients requiring catheter removal	No. of patients switching to haemodialysis	No. of patients requiring catheter replacement	No. of patients with exit-site and tunnel infections	Exit-site and tunnel infection rate	Side-effects of antibiotics	Death due to peritonitis	Hospitalisation rates	Quality of life	Development of antibiotic resistance
Prophylaxis amongst all patients																
Bennett-Jones, 1988[35]										✓						
Bernardini, 1996[40]	✓			✓							✓	✓				
Bernardini, 2005[41,42]	✓		✓	✓				✓		✓	✓	✓				
Cavdar, 2004[43]	✓		✓							✓						✓
Fuchs, 1990[50]										✓	✓					
Gadallah, 2000[44,45]			✓		✓		✓									
Luzar, 1990[3]			✓							✓						
Lye, 1992[36]	✓		✓							✓						
Poole-Warren, 1991[51]	✓	✓	✓							✓						
Sesso, 1988[47]	✓		✓													
Sharma, 1971[37]	✓		✓										✓			
Turner, 1992[52]	✓									✓						
Waite, 1997[46]	✓		✓				✓	✓		✓						
Warady, 2003[53]	✓		✓							✓						
Wilson, 1997[48]			✓					✓		✓		✓				
Wong, 2002[49]										✓						
Wong, 2003[38]	✓		✓				✓			✓						
Zimmerman, 1991[39]	✓		✓	✓						✓	✓					
Treatment of *S. aureus* carriage																
Blowey, 1994[54]	✓		✓							✓						
Muriprocin Study Group, 1996[55,56]	✓		✓	✓			✓	✓		✓	✓	✓				
Perez-Fontan, 1992[57]	✓		✓							✓	✓					
Sesso, 1994[58]	✓		✓	✓			✓			✓	✓	✓	✓			✓

TABLE 6 *Outcomes results for prophylaxis amongst all patients*

Study	Comparison	*S. aureus* carriage at trial entry (no.)	Peritonitis (no.)	Peritonitis rate	Catheter removal (no.)	ESI and/or TI (no.)	ESI and/or TI rate
Antibiotic versus no antibiotic							
Catheter insertion:							
Bennett-Jones, 1988[35]	I.v. gentamicin	–	–	–	–	0/13	–
	No treatment	–	–	–	–	4/13	–
Lye, 1992[36]	I.v. cefazolin and gentamicin	3/25	2/25	–	–	2/25	–
	No treatment	6/25	0/25	–	–	4/25	–
During dialysis:							
Sharma, 1971[37]	Neomycin	–	0/48	–	–	–	–
	Placebo	–	2/41	–	–	–	–
Wong, 2003[38]	Mupirocin ointment	16/73	1/78 (MSSA)	–	0/78	0/78[b]	–
	No treatment	14/81	1/88 (MRSA)	–	0/88	10/88[b]	–
Zimmerman, 1991[39]	Rifampin	9/32	3/32	0.11 mean episodes/patient year	–	3/32[c]	0.22 mean infections/patient year
	No treatment	8/32	3/32	0.16 mean episodes/patient year	–	12/32[c]	0.65 mean infections/patient year
Antibiotic versus antibiotic							
During dialysis:							
Bernardini, 1996[40]	Mupirocin ointment	44%	–	0.04 episodes/dialysis year	–	–	0.13 episodes/dialysis year
	Oral rifampin	44%	–	0.02 episodes/dialysis year	–	–	0.15 episodes/dialysis year
Bernardini, 2005[41]	Mupirocin ointment	9/66	0/66	0 episodes/patient year	–	3/66	0.06 episodes/patient year
	Gentamicin ointment	9/67	2/67	0.03 episodes/patient year	–	5/67	0.08 episodes/patient year
Cavdar, 2004[43]	Mupirocin ointment once weekly	3/18	0/18	–	–	0/18	–
	Mupirocin ointment thrice weekly	0/18	0/18	–	–	0/18	–
Antibiotic versus antibiotic versus no antibiotic							
Catheter insertion:							
Gadallah, 2000[44]	I.v. vancomycin	–	0/90	–	0/90	–	–
	I.v. cefazolin	–	1/88	–	1/88	–	–
	No treatment	–	2/87	–	1/87	–	–
Antiseptic versus no antiseptic							
Catheter insertion:							
Waite, 1997[46]	Povidone–iodine ointment	22/61	0/61	–	1/61	2/61	–
	No treatment	14/56	2/56	–	2/56	8/56	–

continued

TABLE 6 *Outcomes results for prophylaxis amongst all patients (cont'd)*

Study	Comparison	*S. aureus* carriage at trial entry (no.)	Peritonitis (no.)	Peritonitis rate	Catheter removal (no.)	ESI and/or TI (no.)	ESI and/or TI rate
During dialysis:							
Luzar, 1990[3]	Povidone iodine	–	8/74[a]	–	–	15/74[a]	–
	Non-disinfectant soap	–	3/53[a]	–	–	16/53[a]	–
Sesso, 1988[47]	Chorhexidine	–	6/19[d]	–	–	–	–
	Neutral soup	–	4/16[d]	–	–	–	–
Wilson, 1997[48]	Povidone–iodine spray	–	2/77	–	–	9/77	–
	No treatment	–	3/72	–	–	22/72	–
Wong, 2002[49]	Chlorhexidine liquid soap	–	–	–	–	0/69	–
	Pure liquid soap	–	–	–	–	4/48	–
Antiseptic versus antiseptic							
During dialysis:							
Fuchs, 1990[50]	Chlorhexidine	–	–	–	–	1/18	1/134 per patient month
	Sodium hypochlorite	–	–	–	–	2/13	1/41 per patient month
	Povidone–iodine/povidone ointment	–	–	–	–	0/20	–
Other							
During dialysis:							
Poole-Warren, 1991[51]	Vaccination	13/40	8/60	–	–	29/44[e]	–
	Placebo	11/36	8/51	–	–	25/25[e]	–
Turner, 1992[52]	Catheter immobiliser	10/22	–	–	–	4/22[e]	–
	Tape	11/23	–	–	–	4/23[e]	–
	Non-immobilisation	6/21	–	–	–	4/21[e]	–
Warady, 2003[53]	'Flush before fill'	–	7/62[a]	–	–	–	–
	Flushing with 15 ml of sterile dialysate	–	15/59[a]	–	–	–	–

ESI, exit-site infection; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; TI, timed infection.
[a] Denominators are unclear therefore numbers randomised are reported.
[b] 5 × MSSA; 5 × MRSA.
[c] Catheter infections.
[d] Episodes.
[e] Microorganisms.

TABLE 7 S. aureus *nasal carriage versus weeks following vaccination, expressed as number of carriers/group total*[57]

No. of weeks	Vaccination	Placebo
Pre-study	13/40	11/36
7	19/50	14/44
19	11/51	14/46
32	9/29	5/20
44	2/22	6/25
57	10/20	6/22

reported a rash and pruritus at the catheter exit site in five patients allocated to use the povidone–iodine spray. There were no reported side-effects in the group which received no treatment.

Death due to peritonitis caused by *S. aureus*
Only one trial reported this outcome.[37] This trial compared neomycin 0.5 g by mouth or nasogastric tube every 6 hours with a placebo and reported that there were no deaths due to peritonitis caused by *S. aureus*.

Development of antibiotic resistance
One trial[43] comparing mupirocin applied to the exit site once weekly with mupirocin applied three times weekly reported no difference between the groups (one out of seven isolations were resistant to mupirocin in the group applying mupirocin once weekly and one isolation resistant to mupirocin and methicillin in the group applying mupirocin three times weekly).

No data were reported for the following outcomes: peritonitis relapse, number of patients requiring catheter replacement, hospitalisation rates and quality of life.

Oral antibiotics versus no antibiotics
Four trials compared an oral antibiotic with no antibiotics and one trial compared two different types of oral antibiotics with no antibiotic. When considering all oral antibiotics together, there were fewer cases of peritonitis caused by *S. aureus* in the groups which received antibiotics (*Figure 1*: 6/283 versus 7/185: RR 0.69, 95% CI 0.28 to 1.72; $p = 0.43$), but this was not a statistically significant difference. There were also fewer cases of exit-site and/or tunnel infections caused by *S. aureus* (*Figure 2*, 5/70 versus 20/70: RR 0.27, 95% CI 0.11 to 0.65; $p = 0.003$). The direction of effect was similar when considering subcategories (catheter insertion and during dialysis).

Topical antibiotics versus no antibiotics
Only one trial[38] compared the use of a topical antibiotic with no antibiotics. There was no difference in the number of patients with peritonitis caused by *S. aureus*. However, there were 0/78 cases of exit-site and/or tunnel

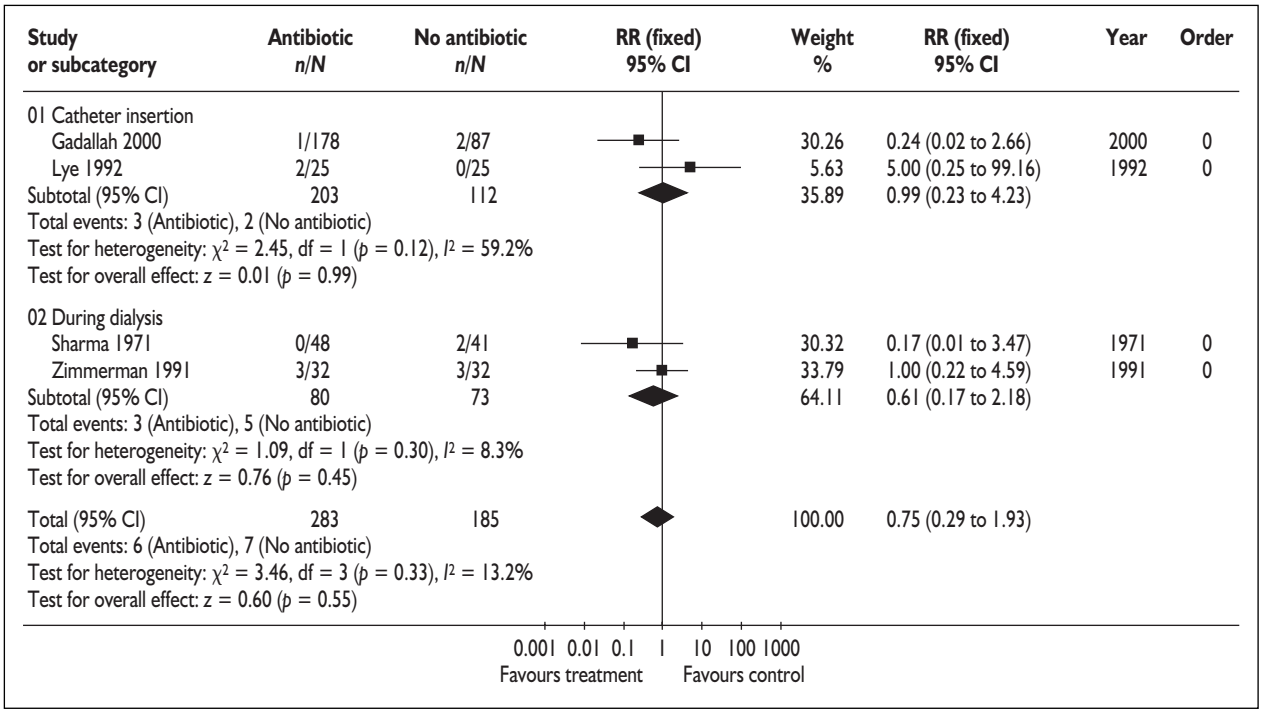

FIGURE 1 *Oral antibiotic prophylaxis amongst all patients: number of patients with peritonitis caused by* S. aureus

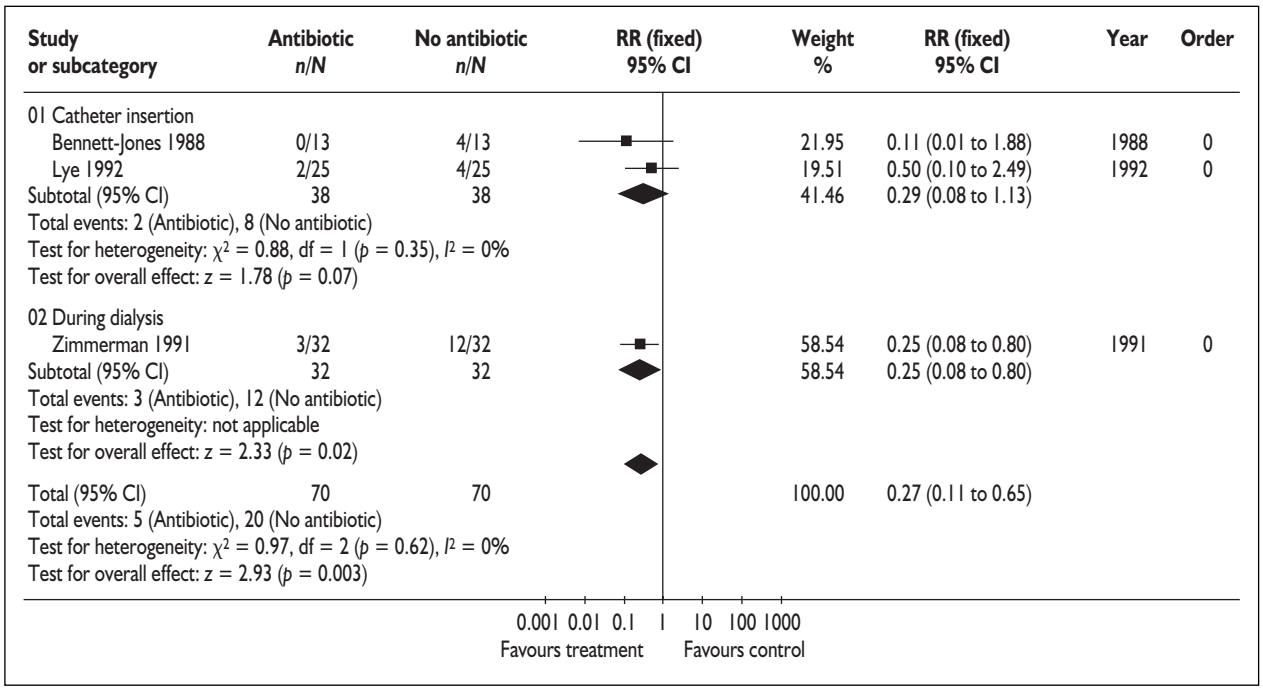

FIGURE 2 *Oral antibiotic prophylaxis amongst all patients: number of patients with exit-site and/or tunnel infections caused by* S. aureus

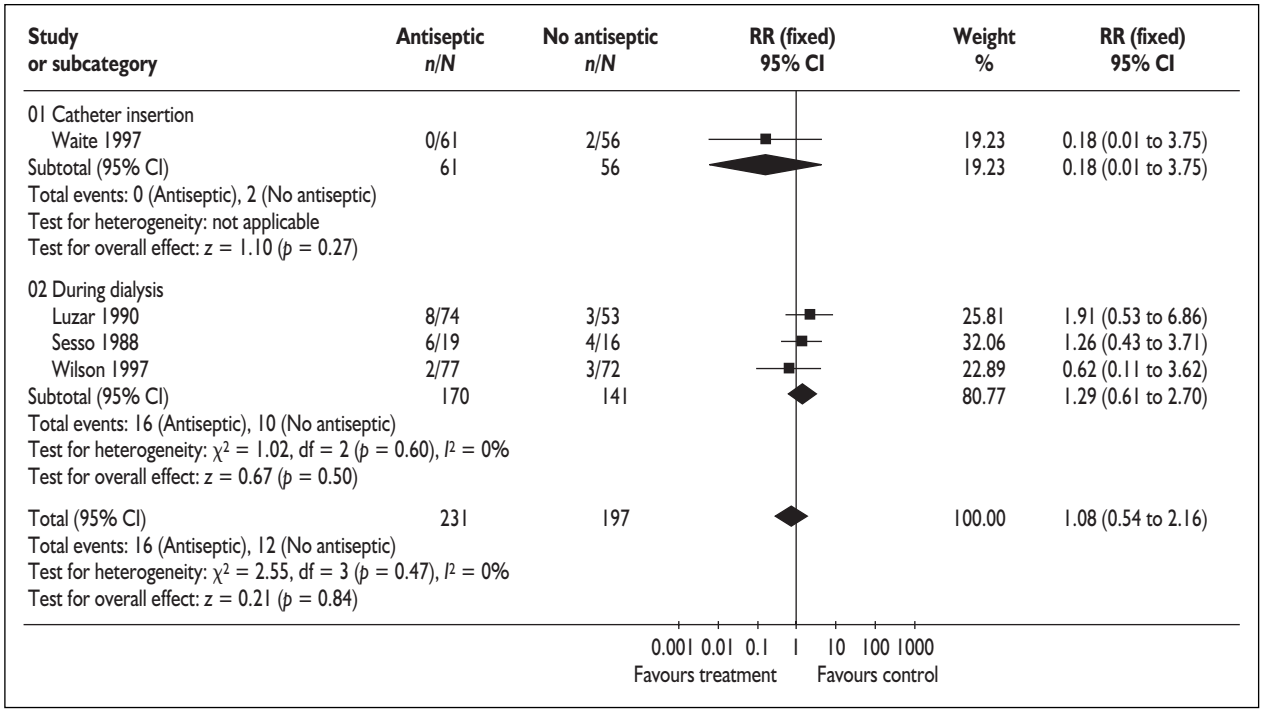

FIGURE 3 *Antiseptic prophylaxis amongst all patients: number of patients with peritonitis caused by* S. aureus

infections in the group allocated to use a topical antibiotic compared with 10/88 cases in the no treatment group [five of which were methicillin-resistant *Staphylococcus aureus* (MRSA) and five were methicillin-sensitive *Staphylococcus aureus* (MSSA)].

Antiseptic versus no antiseptic

When considering all antiseptics together, there were more cases of peritonitis caused by *S. aureus* in the groups allocated to antiseptic use (*Figure 3*: 16/231 versus 12/197: RR 1.08, 95% CI 0.54 to 2.16; $p = 0.84$), but this was not statistically significant.

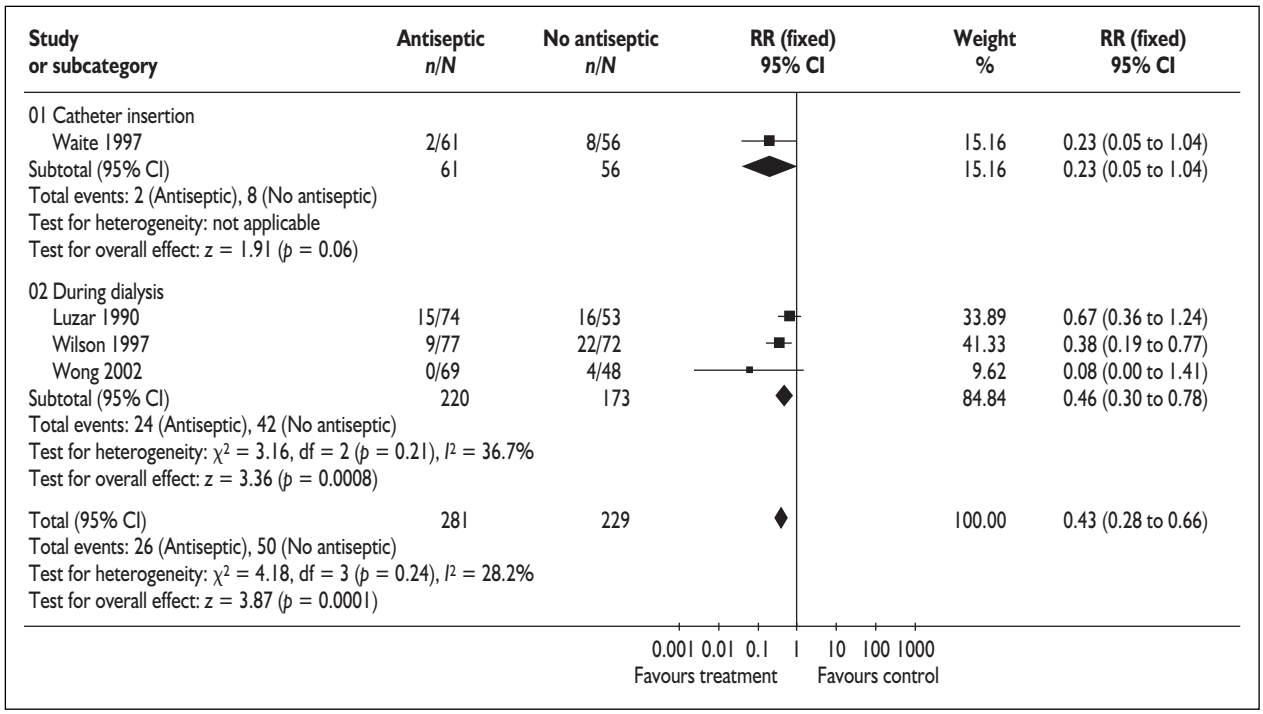

FIGURE 4 *Antiseptic prophylaxis amongst all patients: number of patients with exit-site and/or tunnel infections caused by* S. aureus

However, when considering antiseptic use at the time of catheter insertion, there were fewer cases of peritonitis (one trial). There were fewer cases of exit-site and/or tunnel infections caused by *S. aureus* in the groups allocated to antiseptic use (*Figure 4*, 26/281 versus 50/229: RR 0.43, 95% CI 0.28 to 0.66; $p = 0.0001$). The direction of effect was similar when considering subcategories (catheter insertion and during dialysis).

Treatment of S. aureus *carriage*

Four trials evaluated treatment of *S. aureus* carriage, all during dialysis. Two compared antibiotic treatment with no antibiotic treatment, one trial compared two different antibiotic regimes and one three-armed trial compared two different antibiotic regimes with no antibiotic treatment.

Table 8 provides details, where reported, of the results for the following outcomes: number of patients with *S. aureus* carriage; number of patients with peritonitis; peritonitis rate (number of episodes over total patient months on PD); number of patients requiring catheter removal; number of patients with exit-site and/or tunnel infections; and the exit-site and/or tunnel infection rate.

Time to *S. aureus* carriage

One trial[57] reported time to recolonisation after initial treatment and the results are presented in *Table 9*.

Side-effects

Two trials reported side-effects: the Mupirocin Study Group[55] reported six episodes of side-effects in six patients (one withdrew due to rhinitis) using mupirocin ointment and eight episodes in seven patients (one withdrew due to rhinorrhea and sneezing) using the placebo ointment; and Sesso and colleagues[58] reported that one patient using sodium fusidate ointment discontinued use due to nasal irritation.

Death due to peritonitis caused by *S. aureus*

One trial reporting this outcome[58] reported that there were no deaths due to peritonitis caused by *S. aureus*.

Development of antibiotic resistance

One trial[58] reported that no patient developed ofloxacin-resistant organisms.

There were no data reported for the following outcomes: time to first peritonitis episode; peritonitis relapse; number of patients requiring catheter replacement; hospitalisation rates; and quality of life.

Oral antibiotics versus no antibiotics

Two trials compared oral antibiotics with no antibiotics. When considering all oral antibiotics together, there were fewer cases of peritonitis caused by *S. aureus* in the groups which received

TABLE 8 *Outcomes results for treatment of* S. aureus *carriage*

Study	Comparison	*S. aureus* carriage (no.)	Peritonitis (no.)	Peritonitis rate	Catheter removal (no.)	ESI and/or TI (no.)	ESI and/or TI rate
Antibiotic versus no antibiotic							
During dialysis:							
Blowey, 1994[54]	Oral rifampin plus bacitracin	0/7	0/7	–	–	0/7	–
	No treatment	2/8	2/8	–	–	2/8	–
Mupirocin Study Group, 1996[55,56]	Mupirocin ointment	18/134[a]	18/134[a,b]	1 in 81.8 patient months	3/134[a,b]	9/134	1 in 99.3 patient months
	Placebo ointment	24/133[a]	24/133[a,b]	1 in 53.8 patient months	5/133[a,b]	20/133	1 in 28.1 patient months
Antibiotic versus antibiotic							
During dialysis:							
Perez-Fontan, 1992[57]	Mupirocin nasal ointment	0/12[b]	0/12[b]	–	–	1/12[c]	–
	Neomycin sulphate ointment	1/10[b]	1/10[b]	–	–	1/10[c]	–
Antibiotic versus antibiotic versus no antibiotic							
During dialysis:							
Sesso, 1994[58]	Sodium fusidate ointment	1/9	1/9	0.16	4/9	5/9	0.97
	Oral ofloxacin	4/9	4/9	0.83	3/9	2/9	0.33
	Placebo tablets	5/13	5/13	0.75	6/9	3/13	0.50

[a] Denominators are unclear, therefore numbers randomised are reported.
[b] Episodes.
[c] Catheter infections.

TABLE 9 *Response to treatment and time to recolonisation (months, M)*

Study ID	Comparison	Eradication: no. (%)	+1M	+2M	+3M	+4M	+6M	+10M
Perez-Fontan, 1992[57]	Mupirocin	12 (100)	12 (0)	12 (8)	12 (41)	11 (55)	11 (55)	3 (66)
	Neomycin	10 (40)	4 (0)	4 (25)	4 (75)	–	–	–

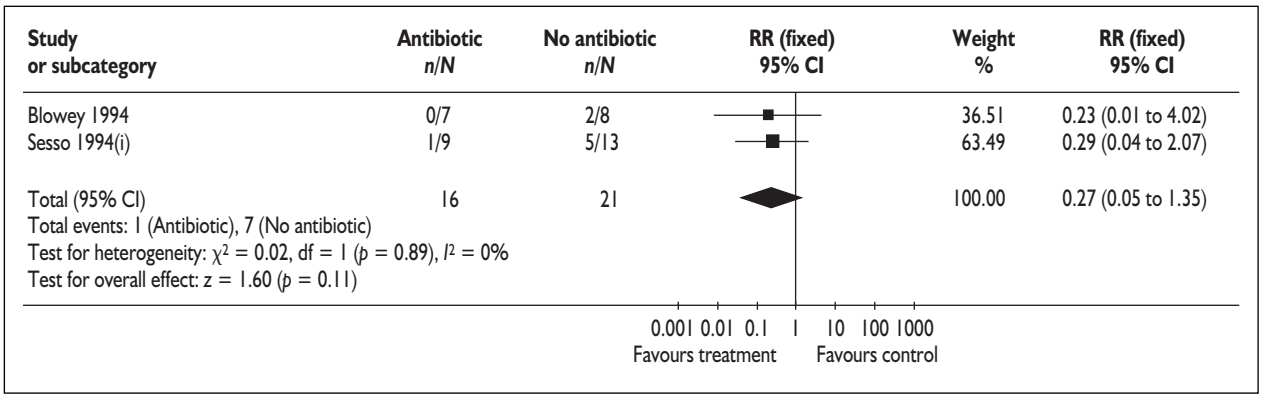

FIGURE 5 *Treatment of* S. aureus *carriage with oral antibiotics: number of patients with peritonitis caused by* S. aureus

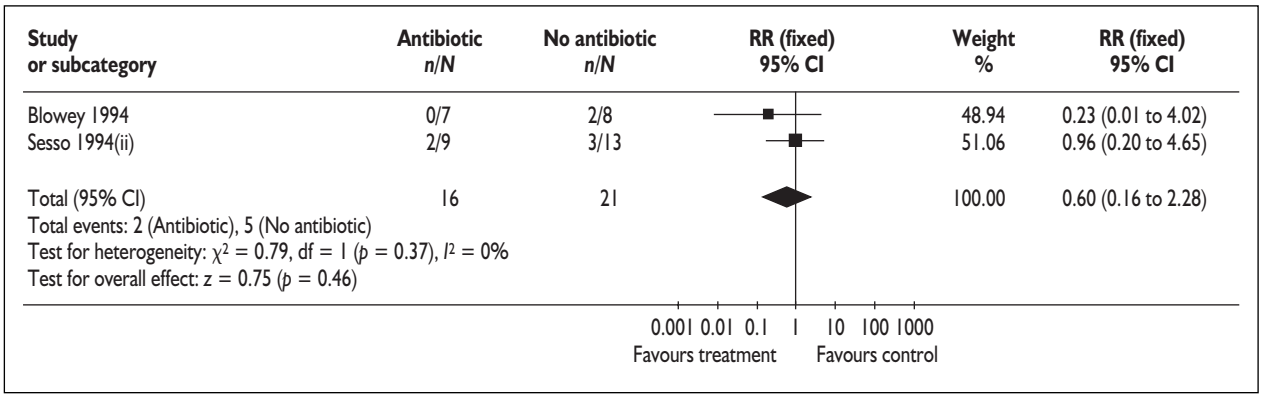

FIGURE 6 *Treatment of* S. aureus *carriage with oral antibiotics: number of patients with exit-site and/or tunnel infections caused by* S. aureus

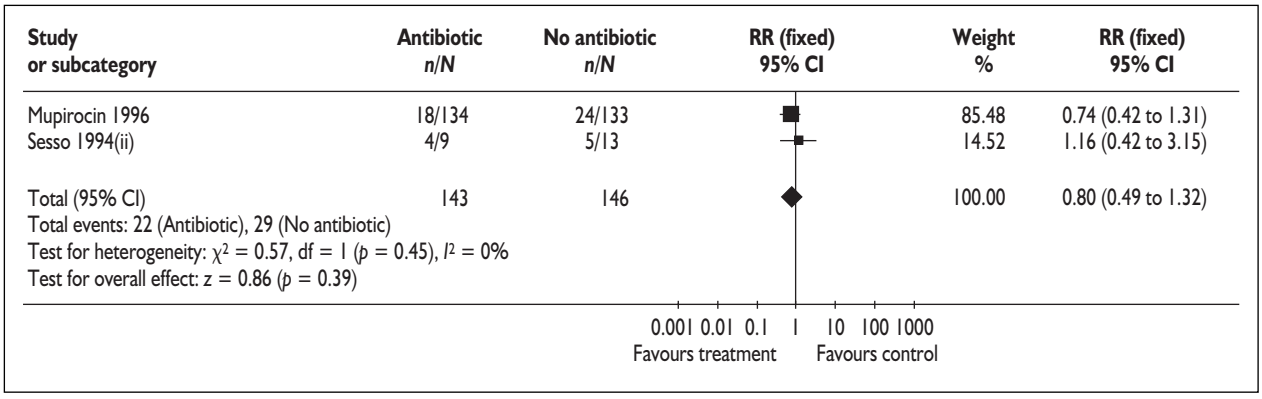

FIGURE 7 *Treatment of* S. aureus *carriage with topical antibiotics: number of patients with peritonitis caused by* S. aureus

antibiotics (*Figure 5*: 1/16 versus 7/21: RR 0.27, 95% CI 0.05 to 1.35; $p = 0.11$) and fewer cases of exit site and/or tunnel infections caused by *S. aureus* (*Figure 6*, 2/16 versus 5/21: RR 0.60, 95% CI 0.16 to 2.28; $p = 0.46$). However, these results were not statistically significant.

Topical antibiotics versus no antibiotics

Two trials compared topical antibiotics with no antibiotics. When considering all topical antibiotics together, there were fewer cases of peritonitis caused by *S. aureus* in the groups which received antibiotics (*Figure 7*: 22/143 versus 29/146: RR 0.80, 95% CI 0.49 to 1.32; $p = 0.39$), fewer patients requiring catheter removal (*Figure 8*, 7/143 versus 11/142: RR 0.63, 95% CI 0.29 to 1.39; $p = 0.26$), and fewer cases of exit site and/or tunnel infections caused by *S. aureus* (*Figure 9*, 14/143 versus 23/146: RR 0.66, 95% CI 0.36 to 1.20; $p = 0.17$). However, these results were not statistically significant.

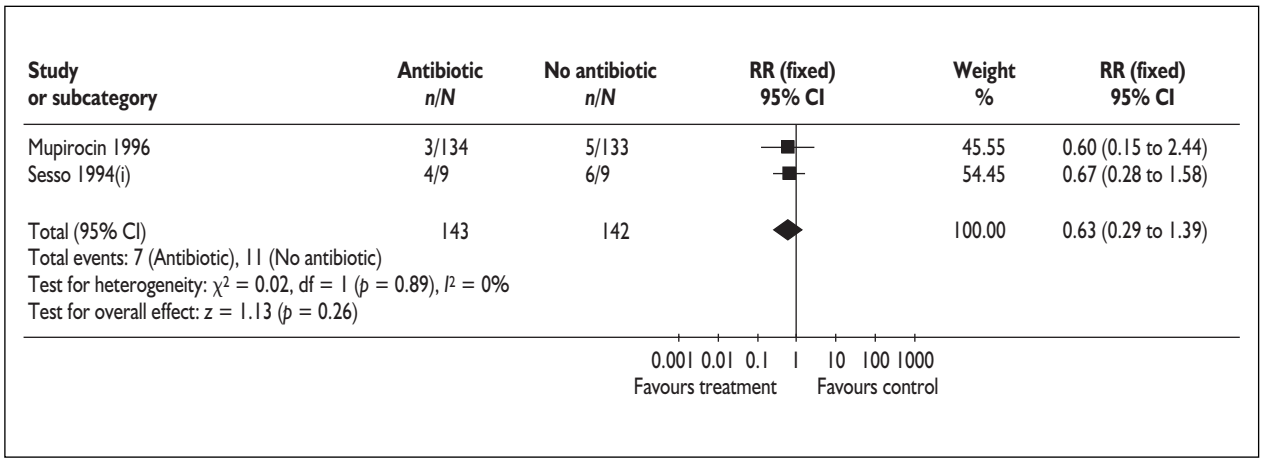

FIGURE 8 *Treatment of* S. aureus *carriage with topical antibiotics: number of patients requiring catheter removal*

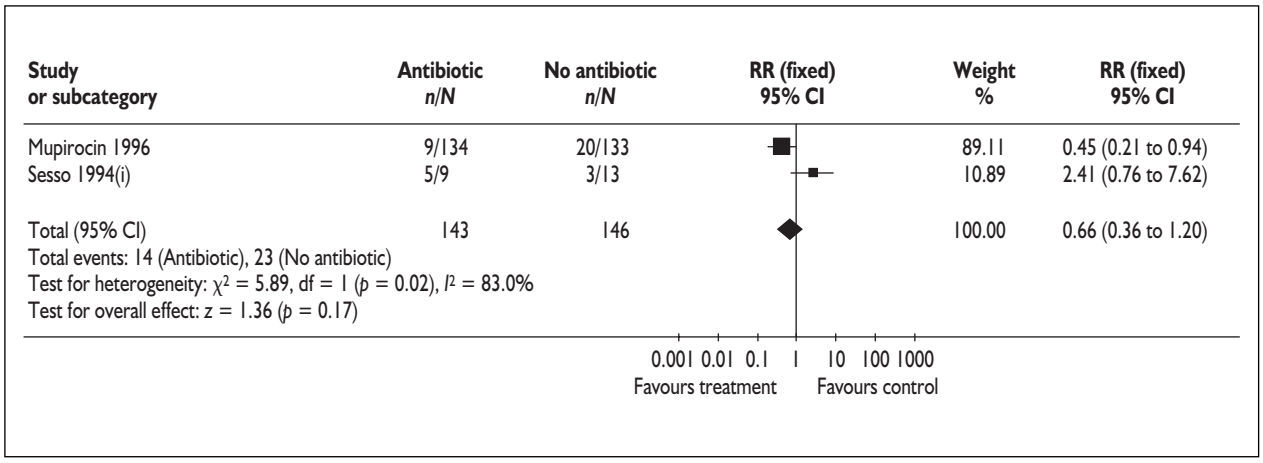

FIGURE 9 *Treatment of* S. aureus *carriage with topical antibiotics: number of patients with exit-site and/or tunnel infections caused by* S. aureus

TABLE 10 *Summary of the clinical effect size*

Outcome	Prophylaxis amongst all		Treatment of *S. aureus* carriage	
	n/N	**RR (95% CI)**	***n/N***	**RR (95% CI)**
Oral antibiotic versus no antibiotic				
Peritonitis (no.)	6/283 vs 7/185	0.75 (0.29 to 1.93)	1/16 vs 7/21	0.27 (0.05 to 1.35)
ESI and/or TI (no.)	(5/70 vs 20/70)	0.27 (0.11 to 0.65)	2/16 vs 5/21	0.60 (0.16 to 2.28)
Topical antibiotic versus no antibiotic				
Peritonitis (no.)	ND	ND	22/143 vs 29/146	0.80 (0.49 to 1.32)
Catheter removal (no.)	ND	ND	7/143 vs 11/142	0.63 (0.29 to 1.39)
ESI and/or TI (no.)	ND	ND	14/143 vs 23/146	0.66 (0.36 to 1.20)
Antiseptic versus no antiseptic				
Peritonitis (no.)	16/231 vs 12/197	1.08 (0.54 to 2.16)	ND	ND
ESI and/or TI (no.)	26/281 vs 50/229	0.43 (0.28 to 0.66)	ND	ND

ND, no data.

Clinical effect size

When considering trials comparing antibiotics with no antibiotics, a summary of the clinical effect size for all outcomes where data were available are given in *Table 10*.

When considering prophylaxis amongst all patients, there is a consistent finding that exit-site and/or tunnel infections are statistically significantly reduced with the use of antibiotics (oral or topical) and antiseptics. However, these findings do not appear to translate into a reduction in peritonitis. To some extent this may reflect the greater frequency of exit-site and/or tunnel infections than peritonitis, and hence lower power for peritonitis, but it does raise the question of how carriage leads to peritonitis.

Chapter 4

Economic evaluation

Introduction

In this chapter, the approach taken to consider the relative cost-effectiveness of interventions to prevent and treat *S. aureus* carriage is presented. A review of previous economic evaluations has not been conducted but one economic evaluation conducted alongside an RCT was identified.[59] This economic evaluation compared prophylactic nasel mupirocin with placebo in patients either starting or established on continuous ambulatory PD. Although this study was generally well conducted and reported, it did not consider the full range of interventions for the prevention and treatment of *S. aureus* carriage. As reported in *Table 8*, the use of the antibiotics reduced the rate of a catheter infection caused by *S. aureus* from one every 28.1 months to one every 99.3 months. The incremental cost per *S. aureus*-related catheter infection prevented in 1994 prices was £187. The costs included the cost of screening and prophylaxis for 1 year and the cost savings arising from the reduced use of therapeutic antibiotics and hospitalisations avoided. Quality-adjusted life-years (QALYs) were not reported as part of this study. Nevertheless, the gain in QALYs required to provide an incremental cost per QALY that society might consider worthwhile (between £20,000 and £30,000 per QALY) would be between 0.0019 and 0.0029. This would be equivalent to between an additional 0.7–1.1 days in full health over 1 year (1 day in full health is equal to 0.00274 QALYs). From this particular study, a judgement would be required as to whether the gains in QALYs estimated could be realised in practice and, even if they can be realised, whether society would be willing to pay for these additional benefits.

The usefulness of the study by Davey and colleagues[59] is that the results indicate that it is not implausible that interventions to prevent or treat *S. aureus* carriage might be cost-effective. Ideally, an economic evaluation comparing all relevant interventions (including the use of a no treatment arm) and utilising the best available evidence would be performed.

The first part of this chapter outlines the framework provided by economic evaluation for informing decision-making. As described in this section, there is insufficient evidence to determine the relative efficiency of the alternative interventions. In response to the limited evidence available, no economic evaluation was performed. However, a hypothetical model is outlined. If sufficient data were available from future research to populate this model, then it would provide an explicit framework to estimate cost-effectiveness.

The economic approach

Relationship between benefits and cost

The objective of economic evaluation is to provide information to assist decision-makers in the allocation of available scarce resources so that benefits can be maximised. The decision to use resources in one way means that the opportunity to use them in other desirable ways is given up. The cost of this decision is the benefits (health gains, etc.) that could have been obtained had the resources been used in another way. The 'opportunity cost' of a decision to use resources in one way is equivalent to the benefits forgone in the best alternative use of these resources. One of the goals of healthcare decision-making is to maximise benefits and minimise opportunity costs. To achieve this, information is required on both resource use (i.e. costs) and benefits (i.e. effectiveness) from alternative courses of action.

Data on effectiveness and costs can be brought together in a matrix format (*Figure 10*) to aid in the judgement about whether a new procedure is preferable to a comparator. In *Figure 10*, it can be seen that, relative to a comparator, the new procedure could achieve (1) greater effectiveness, (2) the same level of effectiveness or (3) less effectiveness. Of course, a fourth option is possible whereby there is not enough evidence to make a judgement on whether the new procedure is more or less effective. In terms of cost, a new procedure could (A) be less costly, (B) result in no difference in costs or (C) be more costly (again, there is the possibility of there being not enough evidence to judge, as represented by row D).

Figure 10 is adapted from that which appeared in early editions of the Cochrane Collaboration Handbook. For any procedure to prevent or treat

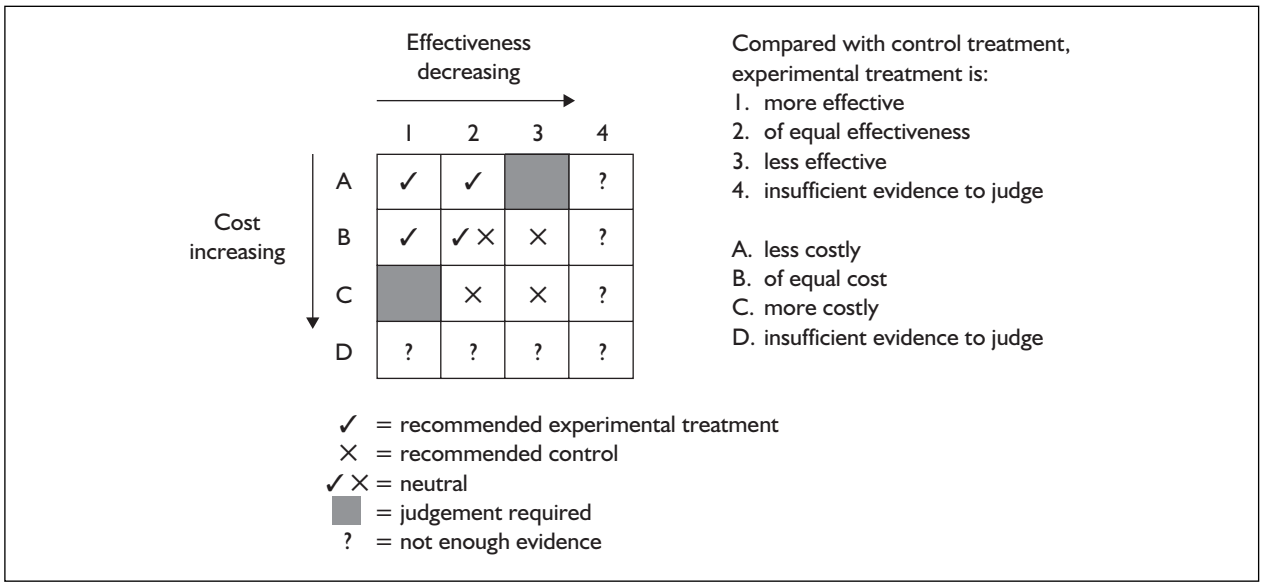

FIGURE 10 *Matrix combining costs and effectiveness*

S. aureus carriage or infection, the optimum position on the matrix is square A1, where an experimental treatment would both save costs and have greater effectiveness relative to current treatment. In squares A1, A2 and B1, the new procedure is more efficient and is assigned a ✓ response to the question of whether it is to be preferred to current practice. In squares B3, C2, and C3 the new procedure is less efficient and thus receives a × response. In squares A3 and C1, a judgement would be required as to whether the more costly procedure is worthwhile in terms of the additional effectiveness gained. Square B2 is neutral, as there is no difference in either costs or effectiveness and other reasons may be needed to justify the adoption of treatment. The areas marked with a **?** response represent situations in which there is not enough evidence on effectiveness, costs or both to judge whether the new procedure is to be preferred.

Consideration of the available evidence

As reported in Chapter 3, the evidence available on relative effectiveness of the alternative methods of preventing or treating *S. aureus* carriage as a means of preventing peritonitis was limited. In terms of the matrix set out in *Figure 10* there is insufficient evidence to draw any conclusions about relative effectiveness (column 4 of the matrix), and hence about the relative cost-effectiveness of any of the interventions (square D4 of the matrix). Additional data collection is required to conduct a formal economic evaluation. The structure for a hypothetical economic model is presented in the next section.

Hypothetical economic model

The methods for a model and its use are illustrated below, and this helps to highlight the areas where additional data would be required before a robust evaluation could be conducted. A Markov model is used to display the temporal and logical sequence of prevention and treatment events. This approach adopted as a Markov model has the ability to represent repetitive events, and the time dependence of both probabilities and utilities which allows for more accurate representation of clinical settings that involve these issues.[60] The model would be designed to estimate costs from the UK NHS perspective and outcomes in terms of QALYs.

This study focuses on patients who receive PD as the initial modality of treatment. A patient who elects or receives PD could over time either die, receive a transplant or transfer to HD. The hypothetical model does not include transplantation and hence may be considered applicable to the majority of patients who, for whatever reason (usually lack of donor organs), do not receive a transplant. As part of the process of developing the model, the parameters needed to assess the cost-effectiveness of alternative interventions were identified. The systematic review of effectiveness reported in Chapter 3, secondary data sources and consultation with clinical experts would provide the parameter estimates. Where such data were likely to be deficient, this has been indicated in the text, to aid future research. The model structure was based on

detailed discussions with clinical members of the review team about the care pathways that patients might follow while on PD and further discussion about how these pathways (and transitions between different modalities of treatment and clinical events) would be influenced by the prevention or treatment of *S. aureus* carriage. The model was then presented to the clinicians and other members of the review team and any relevant changes made to the structure.

Description of the model

The model is made up of a set of health states between which a patient can move over specified periods of time (*Figure 11*). On entry into the model, all patients receive PD. The patient will spend 4 weeks in each state (the cycle length) before facing the possibility of making a transition to another state.

Within the model patients could move into any one of the following states:

1. '*Catheter insertion*'. In this initial state a patient has their peritoneal catheter inserted and begins PD. At the time of their peritoneal catheter insertion the patient may receive a prophylactic intervention or a treatment of *S. aureus* carriage. Following the first 4 weeks after insertion of the catheter, a patient may remain on PD with or without carriage of *S. aureus*. Patients in this state could potentially also develop an infection, transfer to HD or die.
2. '*On PD without SA carriage*'. In this state, the patient receives PD and may also receive routine checks for the development of *S. aureus* carriage. The risk of developing carriage and hence the probability of moving to 'On PD with SA carriage' may be affected by the use of some form of prophylactic preventive treatment either at the time of catheter insertion (the first initial state of the model) or while on dialysis. Patients in this state could potentially also develop an infection, transfer to HD or die.
3. '*On PD with SA carriage*'. Patients in this state are still on PD but are carriers of *S. aureus*. If *S. aureus* carriage were eradicated, the patient would move back to the state 'On PD without SA carriage'. The patient could suffer some form of infection although the risk of this happening may be affected by any of the methods of treating *S. aureus* carriage (antibiotic sprays, ointment or powders). Patients in this state could potentially also transfer to HD or die.
4. '*Infection*'. While on PD, a patient may suffer an exit-site infection, isolated tunnel infection or peritonitis. The infections may occur either separately or sequentially: exit site infection leading to tunnel infection leading to peritonitis. While in this state, patients face the risk of losing their PD tube and moving into temporary or permanent HD. Factors that could make a person move from PD are clearance failure, technique failure or recurrent peritonitis. The types of infection and there effects are:
   (a) Exit-site infection, which is treated with using a local treatment, systemic treatment or catheter change.
   (b) Isolated tunnel infections, which are treated using systemic treatments and/or catheter removal.
   (c) Peritonitis infection, which is mainly due to contamination and is treated with 2 weeks of antibiotics administered peritoneally, intravenously or orally.

   S. aureus infection can be cured without the patient moving from PD (i.e. move to 'On PD without SA carriage'). If *S. aureus* infection is not resolved, the catheter can be removed and the treatment modality switched to 'Temporary HD'. Non-resolution of *S. aureus* infection can be attributed to failure of antibiotics to clear the infection (relapsing peritonitis) or it may arise from an entirely new infection. Relapsing peritonitis can be defined as the recurrence of peritonitis caused by the same organism as the immediately preceding episode of peritonitis within 4 weeks of completion of antibiotic treatment. The model would allow a patient to have a maximum of between two and four infections (i.e. to stay in the state of infection for between two and four cycles) before the PD catheter is removed, in which case the patient would move to the state of 'Temporary HD'.
5. '*Temporary HD*'. As briefly described above, there are several factors that could make a person move from PD, such as clearance failure, technique failure or recurrent peritonitis. Once these factors are resolved some patients may elect to move back to PD. If they are not resolved, a patient may have to stay in HD until they die (and hence move to the state of 'Permanent HD').
6. '*Permanent HD*'. Once a patient enters this state, they do not leave it until they die.
7. '*Dead*' (included as all-cause mortality). This state can be entered from all preceding states.

While the model allows for variation in the parameters of the prevention and treatment of peritonitis across each intervention (either prophylactic prevention of *S. aureus* carriage or

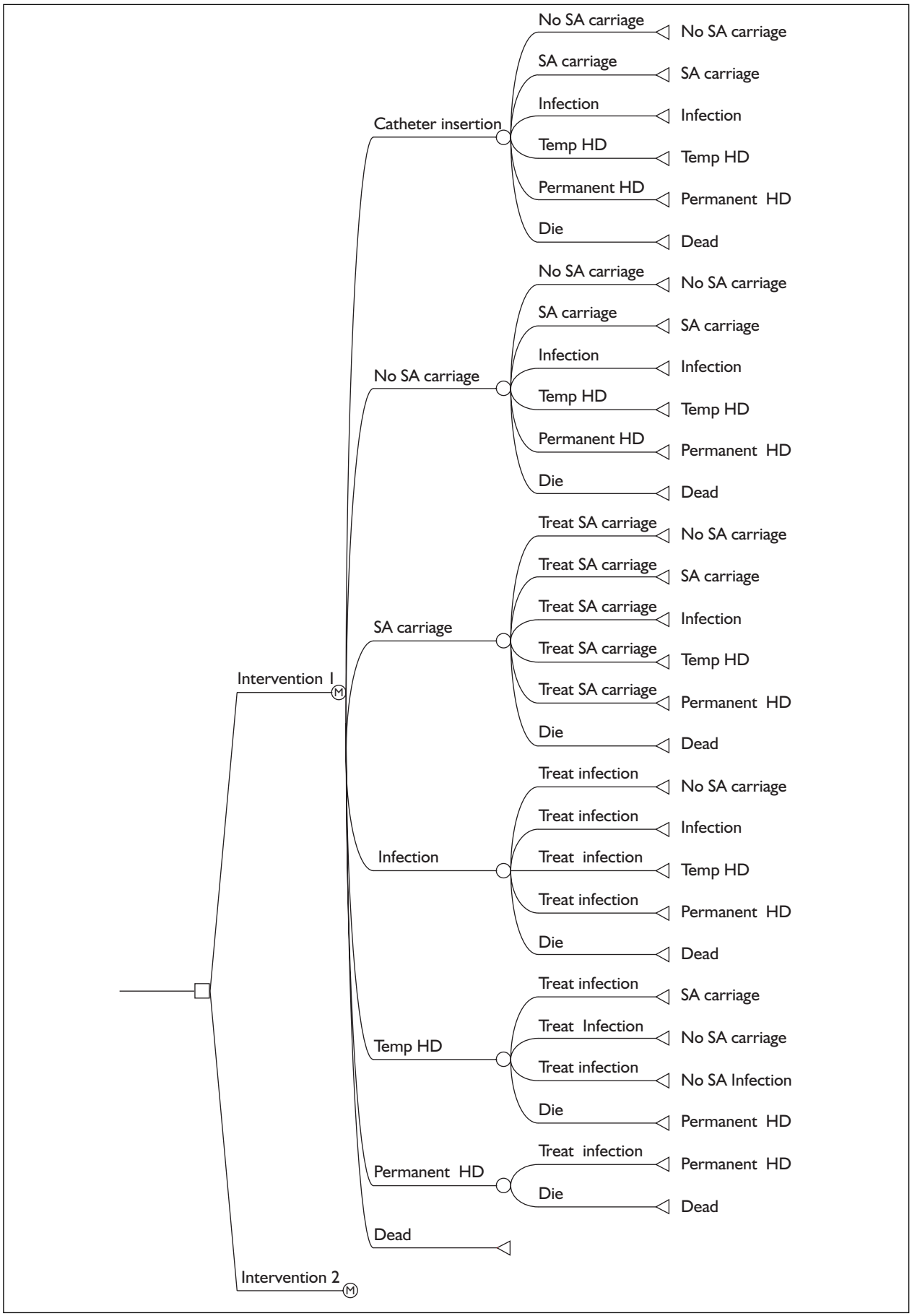

FIGURE 11 *Draft model structure for the estimation of the relative cost-effectiveness of alternative methods to prevent and treat* S. aureus *(SA) carriage*

treatment of *S. aureus* carriage), it is necessary to assume that many parameters will be the same across the different branches. The following section identifies the data required to populate the model. To illustrate this description, the data available for the comparison of the prophylactic use of antibiotics at the time of catheter insertion compared with no treatment have been used.

Estimation of model parameters

A detailed description of the methods that might be used to derive parameters for this model are described in Appendix 7. In brief, this description covers the derivation of transition probabilities, costs and health state utilities.

Assessment of cost-effectiveness

The results of the base-case analysis would be based on the costs and outcomes faced by male and female patients who initially started on PD. If the National Institute for Health and Clinical Excellence (NICE) HTA guidelines were followed, discount rates of 3.5% per annum would be applied to both costs and health benefits.[61] The central outcomes of the analysis and the systematic review would first be presented in terms of a balance sheet. In the balance sheet the incremental differences between the alternative interventions would be presented in their natural units, such as the number of patients with exit-site and/or tunnel infections caused by *S. aureus* and number of patients with peritonitis. The purpose of the balance sheet is to illustrate the trade-offs that would exist when choosing amongst interventions.

Within the economic model, the different outcomes would be combined into a single measure of relative efficiency measured in terms of the incremental cost per QALY. Data on the incremental cost per QALY would be presented in two ways. First, mean costs and QALYs for the alternative interventions could be presented and incremental cost per QALYs calculated where appropriate. The second way in which the cost-effectiveness of the alternative interventions might be presented would be by cost-effectiveness acceptability curves (CEACs). CEACs can be used to illustrate the uncertainty caused by the combined statistical variability in the model's parameter estimates. These curves illustrate the likelihood that a strategy is cost-effective at various threshold values for society's willingness to pay for an additional QALY. It should be noted that in order to be able to perform the probabilistic sensitivity analysis underpinning the estimation of CEACs, all the parameters required for the model should be described by an appropriate statistical distribution that reflects the statistical imprecision surrounding the point estimates (which has not been attempted within this chapter).

Additional analyses

The results of any economic evaluation will be surrounded by uncertainty. In part, this will be reflected by the probabilistic analysis that is proposed above. However, other sensitivity analyses would be required to address the uncertainty around the available data or about the way in which it would be used in the model. In addition to the sensitivity analyses described above, another potential sensitivity analysis might focus on establishing at what point preventing or treating carriage ceases to be cost-effective. Examples of other potential sensitivity analyses are described below.

Risks of S. aureus *carriage, risks of progression to infection and other transition probabilities*

Data on the prevalence of *S. aureus* carriage are not available, yet it is likely that the cost-effectiveness will be dependent on the proportion of people starting PD who are carriers of *S. aureus* and the risks of developing carriage and the consequences of carriage in terms of the development of infections and transitions to other modalities of dialysis.

Costs

The costs of antibiotics identified varied greatly. The most expensive and least expensive costs could be used in the sensitivity analysis. These costs could be varied by increasing/reducing them to establish at what cost prevention or treatment of *S. aureus* carriage and infection ceased to be cost-effective. Similarly, the costs of dialysis would also be varied. This is because costs that would be used in the base-case analysis although coming from a very detailed costing exercise are derived from a small number of centres and so might not be generalisable to the rest of the NHS. The impact of using other relevant costs such as those reported in the NHS reference costs would be explored.

Utilities

The utility data used in the model were based on non-randomised data. These data were based on patient responses to the EQ-5D questionnaire weighted using UK population tariffs. Further analyses could be performed using the utility data from other sources.

Results

Although no formal attempt to conduct the proposed modelling exercise has been made, an

TABLE 11 *Balance sheet of antibiotic versus no antibiotic at catheter insertion and during dialysis*

Favours antibiotic	Favours no intervention	Trials contributing data
Trends towards fewer exit-site and/or tunnel infections (OR 0.15, 95% CI 0.06 to 0.3)	Lower costs	4
No statistically significant difference in number of patients with peritonitis (RR 0.73, 95% CI 0.31 to 1.72)		8
No information on: Numbers of *S. aureus* carriage Number of *S. aureus* cured Number with relapse Modality change rates		

OR, odds ratio; RR, relative risk.

illustration of the limitations of the evidence base is provided by presenting a balance sheet for the comparison of the use of antibiotic versus no antibiotic at catheter insertion (*Table 11*). As can be seen, the data available are very limited and due to the paucity of data no further analyses were carried out.

Summary

In this chapter, a hypothetical model for the comparison of alternative methods to prevent or treat *S. aureus* carriage has been presented. The purpose of this exercise was to consider what information would be required for an economic evaluation and where the main information gaps are. There is insufficient information on the effectiveness and relative effectiveness of the interventions that might be considered. Better data are available for costs and utilities but further data collection would be helpful. In particular, evidence on the utility value for those experiencing any of the infections would be useful.

As the model is hypothetical, the structure outlined in this chapter may need to be adapted to reflect either new knowledge of the care pathways, restrictions imposed by the data available or the nature of the comparisons considered.

Chapter 5
Discussion

Volume of evidence

There is a good number of trials but, as discussed in Chapter 3, the quality of design, or at least of reporting, is not good by today's standards. The first priority is to determine whether treatments are effective, and this requires placebo controls. Many of the trials were of one antibiotic or antiseptic against another. *Table 12* shows those in which there was a placebo arm. The number falls to 13. Some of these were very small, for example those by Bennett-Jones and colleagues[35] with 26 patients, Blowey and colleagues[54] with 15 and Sesso and colleagues[58] with 31 amongst three arms.

A number of the trials show a reduction in exit-site infections but not in the incidence of peritonitis. This may just be a power problem (exit-site infections being much commoner than peritonitis, plus the relatively small numbers involved), but raises the question of the relationship between carriage, infection and peritonitis. It is likely that infection is introduced mainly at exchange via contamination of the tip of the catheter, rather than tracking along the tunnel. Better technique might reduce the risk.

In an observational study, the Scottish Renal Registry Group[62] noted that peritonitis was 15% (95% CI 4 to 26%) less common in units using nasal mupirocin than those not, although this did not apply to *S. aureus* peritonitis (one episode every 106 months in user units versus one every 96 months in non-users; $p = 0.52$).

Other reviews

Our findings are similar to those of the Cochrane Review by Strippoli and colleagues,[63] who also concluded that nasal mupirocin reduces exit-site and tunnel infections, but not peritonitis.

Guideline 3I of the European Guidelines[30] states that, "Use of mupirocin or gentamicin cream at the exit site is recommended to reduce exit site infections", but cites no evidence that this reduces peritonitis. Like the other guidelines, they have to extrapolate from reduction in exit-site infections to reduction in peritonitis.

One issue of concern has been the emergence of resistance to mupirocin, especially in MRSA. Mupirocin became available in 1985[64] and some laboratories have reported increasing numbers of mupirocin-resistant *S. aureus*, especially MRSA.[64] Particularly high resistance rates have been reported from New Zealand, but that may be related to its availability over the counter without prescription.[65] In some European studies, high-level mupirocin resistance was seen in only 2–3% of *S. aureus* isolates,[66,67] but there was variation amongst countries, from 0% in most up to 6% in Belgium and 5% in the UK. Much higher rates have been reported in units with high mupirocin use. In one neonatal intensive care unit, which applied mupirocin routinely to insertion sites of central venous catheters, resistance rates rose over 5 years to 42% of coagulase-negative staphylococci (no results for *S. aureus* were reported), falling again once the routine use was stopped.[68]

TABLE 12 *Summary list of trials of active agents against placebo*

	I.v. antibiotics	Oral antibiotics	Topical antibiotics	Antiseptics
Prophylaxis				
At first insertion	Bennett-Jones, 1988[35] Lye, 1992[36] Gadallah, 2000[45]			Waite, 1997[46]
During later dialysis		Zimmerman, 1991[39] Sharma, 1971[37]	Wong, 2003[38]	Wong, 2002[49] Luzar, 1990[3] Wilson, 1997[48]
Eradication		Blowey, 1994[54] Sesso, 1994[58]	Sesso, 1994[58]	Mupirocin Study Group, 1996[55]

Research needs

As the Cochrane Review said:[63]

> "Given the large number of patients on PD and the importance of peritonitis, the lack of adequately powered RCTs to inform decision-making about strategies to prevent peritonitis is striking."

This is echoed in the UK guidelines:[69]

> "We recommend that a large double-blind placebo controlled study is now needed to confirm whether mupirocin remains useful in clearing carriage in patients or staff when low-level mupirocin resistance is present."

One of their concerns was that eradication of carriage was lower in resistant strains, whether they had high or low level resistance.

The key questions include:

1. What is the natural history and biology of carriage? What are the links between carriage and exit-site infection, and between exit-site infection and peritonitis? How long does carriage last for without treatment? How often is it temporary rather than permanent? The natural history of MRSA carriage suggests that up to half of those colonised will clear spontaneously within 1 year.[70]
2. How do we define carriage? Some centres take swabs from multiple sites. But there is evidence that eradication from the nose reduces carriage elsewhere. Other sites include throat, groin, gut, any wounds and the catheter. Site of carriage seems to be important.
3. Treatment of carriage. Is MSSA relatively harmless? MRSA carriage seems to be a much stronger predictor of infection than MSSA (about 50% by 18 months versus 2% with MSSA).[71] Should the focus be on those with MRSA? Is decolonisation of proven effectiveness, or is recolonisation rapid? Typing of strains could separate relapse from reinfection. Most decolonisation efforts are directed to the nose, which is the most common site of carriage, and to the catheter insertion site, but topical application of antibiotic or antiseptic to these sites will not affect carriage elsewhere, unless carriage elsewhere requires repeated spread of the organism from its more favoured sites. Individual strain type may also be important.
4. What other options for reducing peritonitis might be tried? Would more training help?
5. What factors predict carriage – home contacts, smoking, recent antibiotic treatment, recent hospital admissions? The underlying disease, such as diabetes, may affect susceptibility to infection.

Eradication topics include:

- intermittent versus chronic
- antiseptics versus antibiotics
- the choice of drug
- is vaccination worth revisiting?

The design of any intervention trial should consider confounding factors such as type of catheter, training and automated PD versus ambulatory PD.

The choice of antibiotic(s) to be tested in trials should take into account susceptibility of individual strains, and these may vary amongst different dialysis centres. MRSA rates also vary, and its presence is likely to compromise the benefits of any β-lactam antibiotic. MRSA strains also vary in their susceptibility to other key antibiotics such as gentamicin, rifampicin, fucidin, neomycin and mupirocin, though probably not to antiseptics. Long-term studies would be needed to monitor the emergence of resistance – this is high risk for agents such as mupirocin and rifampicin. Some agents such as mupirocin, rifampicin and fucidin are active mainly against Gram-positive infections.

The widespread use of mupirocin, and the concerns about resistance, make it a high priority for research.

The key outcomes of research into prevention would be:

- Episodes of peritonitis – average number per patient per annum in population on PD in each unit.
- Patient-based data – number of patients having one or more episodes per annum, or over a longer period; time from first insertion of catheter to first episode of peritonitis. Even if the number of infections was the same, delaying infection would be a useful outcome.
- Numbers of temporary transfers to HD.
- Duration of successful treatment on PD. Repeated episodes of peritonitis will shorten the life of the peritoneal membrane as a dialysis membrane.

Chapter 6
Conclusions

The importance of peritonitis in PD is not in doubt, and it remains the main cause of transfer to HD. The evidence on prevention is disappointing: exit-site infections are reduced but not peritonitis, although this may be because the studies were too small or too short, or because the incidence of peritonitis was low. There is also some concern about the development of resistance to mupirocin amongst MRSA strains. More research is required.

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Contribution of authors

Kirsty McCormack (Research Fellow), Linda McIntyre (Systematic Reviewer), Sian Thomas (Systematic Reviewer) and Helen Rothnie (Systematic Reviewer) carried out the assessment of studies for inclusion and data extraction. Kirsty McCormack completed the review of effectiveness. Mary Kilonzo (Research Fellow) conducted the economic evaluation under supervision by Luke Vale (Senior Research Fellow). Cynthia Fraser (Information Officer) developed and ran the search strategies, and was responsible for obtaining papers and for reference management. Kannaiyan Rabindranath (Specialist Registrar in Nephrology) drafted the protocol and the introduction and provided specialist renal advice. Nick Fluck (Consultant Nephrologist) and Ian Gould (Consultant Microbiologist) provided expert advice on renal and microbiological aspects, respectively. Norman Waugh (Professor of Public Health; methodology adviser) provided clinical and methodological advice and commented on drafts of the review.

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Appendix 1

Search strategies

The following search strategies were used to identify reports of RCTs and systematic reviews evaluating the effectiveness of preventing and treating *Staphylococcus aureus* carriage on peritoneal catheter-related infections.

MEDLINE (1996–November Week 3 2005), EMBASE (1980–Week 1 2006) (MEDLINE Extra 6 January 2006)
Ovid Multifile Search. URL: http://gateway.ovid.com/athens

1 exp peritoneal dialysis/
2 continuous ambulatory peritoneal dialysis/ use emez
3 peritoneal dialysis.tw.
4 (capd or ccpd or apd).tw.
5 or/1-4
6 staphylococcal infections/pc
7 peritonitis/pc
8 bacterial peritonitis/pc use emez
9 catheterization/ae use mesz
10 catheterization/ use emez
11 catheters, indwelling/ae use mesz
12 indwelling catheter/ use emez
13 surgical wound infection/ use mesz
14 surgical infection/ use emez
15 catheter exit$.tw.
16 exit site$.tw.
17 (catheter adj3 infect$).tw.
18 (catheter adj3 infect$).tw.
19 (tunnel adj3 infect$).tw.
20 or/13-19
21 (prevent$ or prophyla$ or reduc$ or limit$).tw.
22 20 and 21
23 or/6-12,22
24 5 and 23
25 staphylococcus aureus/
26 bacterium carrier/ use emez
27 bacterial colonization/ use emez
28 methicillin resistance/ use mesz
29 vancomycin resistance/ use mesz
30 methicillin resistant staphylococcus aureus/ use emez
31 aureus.tw.
32 (msra or mssa or visa or vrsa).tw.
33 (carriage or carrier$ or host$).tw.
34 (colony or coloni?ation).tw.
35 33 or 34
36 or/25,28-32
37 35 and 36
38 or/26-27,37
39 5 and 38
40 antibiotic prophylaxis/
41 exp anti-infective agents/
42 or/40-41
43 5 and (25 or 31) and 42
44 24 or 39 or 43
45 animal/ not human/ use mesz
46 (animal/ or nonhuman/) not human/ use emez
47 44 not (45 or 46)
48 clinical trial.pt. use mesz
49 exp controlled clinical trials/ use mesz
50 randomised controlled trial/ use emez
51 clinical trial/ use emez
52 random allocation/ use mesz
53 randomization/ use emez
54 placebo effect/ use mesz
55 placebo/ use emez
56 random$.tw.
57 placebo$.tw.
58 or/48-57
59 meta analysis.tw.
60 meta analysis.pt. use mesz
61 meta analysis/ use emez
62 review.ab.
63 review.pt. use mesz
64 systematic review/ use emez
65 or/60-65
66 47 and (59 or 66)
67 67 and eng.la.
68 remove duplicates from 68

CINAHL (1982–December Week 2 2005)
Ovid Multifile Search. URL: http://gateway.ovid.com/athens

1 exp peritoneal dialysis/
2 peritoneal dialysis.tw.
3 (capd or ccpd or apd).tw.
4 or/1-3
5 staphylococcal infections/pc
6 peritonitis/pc
7 catheterization/ae
8 catheters, dialysis/ae
9 catheter-related infections/
10 catheter exit$.tw.
11 exit site$.tw.
12 (catheter adj3 infect$).tw.
13 (tunnel adj3 infect$).tw.

14 or/9-13
15 prevent$ or prophyla$ or reduc$ or limit$).tw.
16 14 and 15
17 or/5-8,16
18 4 and 17
19 Staphylococcus Aureus/
20 methicillin resistance/
21 vancomycin resistance/
22 aureus.tw.
23 (msra or mssa or visa or vrsa).tw.
24 bacterial colonization/
25 carrier state/
26 (carriage or carrier$ or host$).tw.
27 (colony or coloni?ation).tw.
28 or/25-27
29 or/19-23
30 28 and 29
31 24 or 30
32 4 and 31
33 antibiotic prophylaxis/
34 exp antiinfective agents/
35 or/33-34
36 4 and (19 or 22) and 35
37 18 or 32 or 36
38 37 and eng.lg.

Science Citation Index (1985–7 January 2006)
SCI Proceedings (1990–6 January 2006)
Web of Knowledge URL: http://wok.mimas.ac.uk/

#1 TS=(capd OR ccpd OR apd)
#2 TS=(peritoneal SAME dialysis)
#3 #1 OR #2
#4 TS=(coloni* SAME (aureus OR msra OR mssa OR visa OR vrsa))
#5 TS=(colony SAME (aureus OR msra OR mssa OR visa OR vrsa))
#6 TS=(host* SAME (aureus OR msra OR mssa OR visa OR vrsa))
#7 TS=(carrier* SAME (aureus OR msra OR mssa OR visa OR vrsa))
#8 TS=(carriage SAME (aureus OR msra OR mssa OR visa OR vrsa))
#9 TS=((methicillin OR vancomycin) SAME resist*)
#10 #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11 #3 AND #10
#12 TS=((prevent* OR prophyla* OR reduc* OR limit*) SAME staphylococcal)
#13 TS=((prevent* OR prophyla* OR reduc* OR limit*) SAME aureus)
#14 TS=((prevent* OR prophyla* OR reduc* OR limit*) SAME peritonitis)
#15 TS=(catheter* SAME infect*)
#16 TS=(tunnel SAME infect*)
#17 TS=(exit* SAME (catheter* OR site*))
#18 #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19 #3 AND #18
#20 #11 OR #19
#21 TS=randomized
#22 TS=randomised
#23 TS=random
#24 TS=randomly
#25 TS=random* assign*
#26 TS=random* alloc*
#27 TS=(control* SAME trial*)
#28 TS=meta analysis
#29 TS=systematic review*
#30 #20 AND (#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)

DocType=All document types; Language=All languages

BIOSIS (1985–3 January 2006)
Edina URL: http://edina.ac.uk/biosis/

((((((al: (meta analysis) or al: (systemtic review*)) and ()) or ((al: (random or randomly) or al: (control* n3 trial*)) and ())) or ((al: (randomized or randomised) or al: (random* alloc*) or al: (random* assign*)) and ()))) and (((((((((al: (exit* n3 catheter*) or al: (exit* n3 site*)) and ()) or ((al: (catheter* n3 infect*) or al: (tunnel n3 infect*)) and ())) or ((al: (prevent* or prophyla* or reduc* or limit*) and al: (staphylococcal or aureus or peritonitis)) and ()))) and ((((al: (peritoneal n3 dialysis)) and ()) or ((al: (capd) or al: (ccpd) or al: (apd)) and ())))))) or ((((((al: (methicillin n3 resist*) or al: (vancomycin n3 resist*)) and ()) or (al: (aureus or mrsa or mssa or visa or vrsa) and al: (carriage or carrier* or host* or colony or coloni*)))) and ((((al: (peritoneal n3 dialysis)) and ()) or ((al: (capd) or al: (ccpd) or al: (apd)) and ()))))))))

Clinical Trials (December 2005)
URL: http://clinicaltrials.gov/ct/gui/c/r
Current Controlled Trials (December 2005)
URL: http://www.controlled-trials.com/

Aureus AND (peritoneal OR CAPD)

Cochrane Library Issue 4, 2005
URL: http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME
National Research Register (Issue 4, 2005)
URL: http://www.update-software.com/National/

#1 MeSH descriptor Peritoneal Dialysis explode all trees in MeSH products
#2 peritoneal dialysis in All Fields in all products

#3 capd in All Fields or ccpd in All Fields or apd in All Fields in all products
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Staphylococcal Infections explode all trees with qualifier: PC in MeSH products
#6 MeSH descriptor Peritonitis explode all trees with qualifier: PC in MeSH products
#7 MeSH descriptor Catheterization explode all trees with qualifier: AE in MeSH products
#8 MeSH descriptor Catheters, Indwelling explode all trees with qualifier: AE in MeSH products
#9 MeSH descriptor Surgical Wound Infection explode all trees in MeSH products
#10 exit site* in All Fields or catheter NEAR/3 infect* in All Fields or tunnel NEAR/3 infect* in All Fields or catheter exit* in All Fields in all products
#11 (#9 OR #10)
#12 prevent* in All Fields or prophyla* in All Fields or reduc* in All Fields or limit* in All Fields in all products
#13 (#11 AND #12)
#14 (#5 OR #6 OR #7 OR #8 OR #13)
#15 (#4 AND #14)
#16 MeSH descriptor Staphylococcus aureus explode all trees in MeSH products
#17 aureus in All Fields in all products
#18 mrsa in All Fields or mssa in All Fields or visa in All Fields or vrsa in All Fields in all products
#19 MeSH descriptor Methicillin Resistance explode all trees in MeSH products
#20 MeSH descriptor Vancomycin Resistance explode all trees in MeSH products
#21 carriage in All Fields or carrier* in All Fields or host* in All Fields in all products
#22 colony in All Fields or colonization in All Fields or colonisation in All Fields in all products
#23 (#16 OR #17 OR #18 OR #19 OR #20)
#24 (#21 OR #22)
#25 (#23 AND #24)
#26 (#4 AND #25)
#27 MeSH descriptor Antibiotic Prophylaxis explode all trees in MeSH products
#28 MeSH descriptor Anti-Infective Agents explode all trees in MeSH products
#29 (#27 OR #28)
#30 (#16 OR #17)
#31 (#4 AND #29 AND #30)
#32 (#15 OR #26 OR #31)

DARE and HTA Databases (December 2005)
NHS Centre for Reviews and Dissemination
URL: http://nhscrd.york.ac.uk/welcome.htm

Peritoneal-dialysis (exploded) or capd
and
aureus

Conference proceedings abstracts screened

1st Asian Chapter Meeting ISPD, Hong Kong, December 2002, *Perit Dial Int* 2003;**23**(Suppl 2).
2nd Asian Chapter Meeting, Hyderabad, India, January 2005, *Perit Dial Int* 2005;**25**(Suppl 2).
1st Joint ISPD/EUROPD Congress, Amsterdam, August 2004, *Perit Dial Int* 2004;**24**(Suppl 2).

Journals full text screened

Peritoneal Dialysis International (1981–2005)
Advances in Peritoneal Dialysis (1985–2004)

Appendix 2

Study eligibility form

Effectiveness of preventing and treating *Staphylococcus aureus* carriage on peritoneal catheter-related infections

Study ID: _____ Refman ID: _____

Type of study

Q1. Is the study a randomised controlled trial or a quasi-randomised controlled trial?

Yes ⇩ **Go to Next question** | **Unclear** ⇩ **Go to Next question** | **No** ⇩ Exclude

Participants in the study

Q2. Were the participants in the study adult or paediatric patients undergoing peritoneal dialysis or about to undergo a peritoneal catheter placement procedure?

Yes ⇩ **Go to Next question** | **Unclear** ⇩ **Go to Next question** | **No** ⇩ Exclude

Interventions in the study

Q3. Did one group receive antimicrobial treatment, antiseptic medication or other intervention to prevent or treat *S. aureus* carriage?

Yes ⇩ **Go to Next question** | **Unclear** ⇩ **Go to Next question** | **No** ⇩ Exclude

Q4. Did another group receive a different intervention or no treatment to prevent or treat S. aureus carriage?

Yes ⇩ **Go to Next question** | **Unclear** ⇩ **Go to Next question** | **No** ⇩ Exclude

Outcomes in the study

Q5. Did the study report any of the pre-specified outcomes (refer to data abstraction and quality assessment form)

Yes ⇩ **Include, subject to clarification of 'unclear' points** | **Unclear** ⇩ **Include, subject to clarification of 'unclear' points** | **No** ⇩ Exclude

Final decision:

Include trial ☐ Background information ☐ Economic data ☐ Systematic review ☐

Unclear ☐ Exclude ☐

Appendix 3

Data abstraction and quality assessment form

Effectiveness of preventing and treating *Staphylococcus aureus* carriage on peritoneal catheter-related infections

Reviewer ID: _____

Study Details

Study ID: Abstract ☐ Full text ☐ Unpublished ☐

Authors: _____

_____

Title: _____

_____

Publication year or date of interim data collection: _____

Study Design

RCT ☐ **Quasi RCT** ☐

Prevention trial ☐ **Treatment trial** ☐

Randomisation details _____

Quality assessment

Allocation concealment:	Adequate ☐	Inadequate ☐	Unclear ☐
Blinding:			
Blinding of investigators:	Yes ☐	No ☐	Unclear ☐
Blinding of participants:	Yes ☐	No ☐	Unclear ☐
Blinding of outcome assessor:	Yes ☐	No ☐	Unclear ☐
Blinding of data analysis:	Yes ☐	No ☐	Unclear ☐
Intention to treat analysis:			
Stated & confirmed ITT ☐		**Not stated but confirmed ITT** ☐	
Not stated but confirmed <u>not</u> ITT ☐		**Stated but not confirmed <u>not</u> ITT** ☐	
		Not stated ☐	
Participants lost to follow-up	Yes ☐	No ☐	Unclear ☐

Percent of participants excluded or lost to follow-up: _____

Participants	
Number of participants randomised or included in trial: _____	
Proportion of numbers in clinic included in trial: _____	
Criteria for inclusion:	Criteria for exclusion:

Setting and Timing
Setting of study: _____
Recruitment period: _____
Follow-up period: _____

Screening and treatment of nasal *S. aureus*
Screening: _____
_____
Treatment _____
_____

Interventions		
	Treatment/Prevention	No of patients
Intervention 1 _____	_____	_____
Intervention 2 _____	_____	_____
Intervention 3 _____	_____	_____

Patient Characteristics			
	Intervention 1	**Intervention 2**	**Intervention 3**
Age (years)			
Sex (M/F)			
Adults (No)			
Paediatrics (No)			
Diabetic Nephropathy (No)			
Hypertension and Renovascular Disease (No)			
Glomerulonephritis (No)			
Adult Polycystic Kidney Disease (No)			
Reflux Nephropathy (No)			
E coli 0157 (No)			
Other aetiology (No & specify)			
Time on PD before treatment			
Indications of infirmity (specify)			
Hygiene measures taken (specify)			

Outcomes			
	Intervention 1	**Intervention 2**	**Intervention 3**
No of patients with *S. aureus* carriage			
Time to *S. aureus* carriage			
No of patients with peritonitis			
Peritonitis rate (no of episodes over total pt months on PD)			
Time to first peritonitis episode			
Peritonitis relapse (No & specify time to)			
No of patients requiring catheter removal			
No of patients switching to haemodialysis			
No of patients requiring catheter replacement			
No of patients with exit-site and tunnel infections			
Exit-site and tunnel infection rate			
Side effects of antibiotics			
Death due to peritonitis			
Hospitalisation rates			
Quality of life			
Development of antibiotic resistance			

Appendix 4

List of included studies

Bennett-Jones, 1988
Bennett-Jones DN, Martin J, Barrett A, Duffy TJ, Naish PF, Aber GM. Prophylactic gentamicin in the prevention of early exit-site infections and peritonitis in CAPD. *Adv Perit Dial* 1988;**4**:147–50.

Bernardini, 1996
Bernardini J, Piraino B, Holley J, Johnston JR, Lutes R. A randomized trial of *Staphylococcus aureus* prophylaxis in peritoneal dialysis patients: mupirocin calcium ointment 2% applied to the exit site versus cyclic oral rifampin. *Am J Kidney Dis* 1996;**27**:695–700.

Bernardini, 2005
Primary reference
Bernardini J, Bender F, Florio T, Sloand J, Palmmontalbano L, Fried L, *et al*. Randomized, double-blind trial of antibiotic exit site cream for prevention of exit site infection in peritoneal dialysis patients. *J Am Soc Nephrol* 2005;**16**:539–45.

Secondary reference
Bernardini J, Fried L, Bender F, Sloand J, Palmmontalbano L, Florio T, *et al*. A randomized double-blind trial of PD infection comparing mupiocin to gentamicin sulfate cream. *Perit Dial Int* 2004; **24**(Suppl 2):S53.

Blowey, 1994
Blowey DL, Warady BA, McFarland KS. The treatment of *Staphylococcus aureus* nasal carriage in pediatric peritoneal dialysis patients. *Adv Perit Dial* 1994;**10**:297–9.

Cavdar, 2004
Cavdar C, Zeybel M, Atay T, Sifil A, Sanlidag C, Gulay Z, *et al*. The effects of once- or thrice-weekly mupirocin application on mupirocin resistance in patients on continuous ambulatory peritoneal dialysis – first 6 months' experience. *Adv Perit Dial* 2004;**20**:62–6.

Fuchs, 1990
Fuchs J, Gallagher ME, Jackson-Bey D, Krawtz D, Schreiber MJJ. A prospective randomized study of peritoneal catheter exit-site care. *Dial Transplant* 1990; **19**:81–4.

Gadallah, 2000
Primary reference
Gadallah MF, Ramdeen G, Torres C, Mignone J, Patel D, Mitchell L, *et al*. Preoperative vancomycin prophylaxis for newly placed peritoneal dialysis catheters prevents postoperative peritonitis. *Adv Perit Dial* 2000;**16**:199–203.

Secondary reference
Gadallah MF, Ramdeen G, Mignone J, Patel D, Mitchell L, Tatro S. Role of preoperative antibiotic prophylaxis in preventing postoperative peritonitis in newly placed peritoneal dialysis catheters. *Am J Kidney Dis* 2000;**36**:1014–19.

Luzar, 1990
Luzar MA, Brown CB, Balf D, Hill L, Issad B, Monnier B, *et al*. Exit-site care and exit-site infection in continuous ambulatory peritoneal dialysis (CAPD): results of a randomized multicenter trial. *Perit Dial Int* 1990;**10**:25–9.

Lye, 1992
Lye WC, Lee EJ, Tan CC. Prophylactic antibiotics in the insertion of Tenckhoff catheters. *Scand J Urol Nephrol* 1992;**26**:177–80.

Mupirocin Study Group, 1996
Primary reference
Mupirocin Study Group. Nasal mupirocin prevents *Staphylococcus aureus* exit-site infection during peritoneal dialysis. Mupirocin Study Group. *J Am Soc Nephrol* 1996; **7**:2403–8.

Secondary reference
Davey P. Randomised clinical trial and cost analysis of mupirocin for prevention of exit site infections (ESI) in continuous ambulatory peritoneal dialysis (CAPD). *Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy* 1996;**36**:296.

Perez-Fontan, 1992
Perez-Fontan M, Rosales M, Rodriguez-Carmona A, Moncalian J, Fernandez-Rivera C, Cao M, *et al*. Treatment of *Staphylococcus aureus* nasal carriers in CAPD with mupirocin. *Adv Perit Dial* 1992;**8**:242–5.

Poole-Warren, 1991
Poole-Warren LA, Hallett MD, Hone PW, Burden SH, Farrell PC. Vaccination for prevention of CAPD associated staphylococcal infection: results of a prospective multicentre clinical trial. *Clin Nephrol* 1991; **35**:198–206.

Sesso, 1988
Sesso R, Barbosa D, Sato I, Draibe S, Castelo A, Ajzen H. A randomized controlled trial to assess the effectiveness of daily baths with 4% chlorhexidine gluconate vs neutral soap in CAPD patients. *Perit Dial Int* 1988;**8**:288.

Sesso, 1994
Sesso R, Parisio K, Dalboni A, Rabelo T, Barbosa D, Cendoroglo M, *et al*. Effect of sodium fusidate and ofloxacin on *Staphylococcus aureus* colonization and infection in patients on continuous ambulatory peritoneal dialysis. *Clin Nephrol* 1994;**41**:370–6.

Sharma, 1971
Sharma BK, Rodriguez H, Gandhi VC, Smith EC, Pillay VK, Dunea G. Trial of oral neomycin during peritoneal dialysis. *Am J Med Sci* 1971;**262**:175–8.

Turner, 1992
Turner K, Edgar D, Hair M, Uttley L, Sternland R, Hunt L, *et al*. Does catheter immobilization reduce exit-site infections in CAPD patients? *Adv Perit Dial* 1992; **8**:265–8.

Waite, 1997
Waite NM, Webster N, Laurel M, Johnson M, Fong IW. The efficacy of exit site povidone–iodine ointment in the prevention of early peritoneal dialysis-related infections. *Am J Kidney Dis* 1997;**29**:763–8.

Warady, 2003
Warady BA, Ellis EN, Fivush BA, Lum GM, Alexander SR, Brewer ED, *et al*. "Flush before fill" in children receiving automated peritoneal dialysis. *Perit Dial Int* 2003;**23**:493–8.

Wilson, 1997
Wilson AP, Lewis C, O'Sullivan H, Shetty N, Neild GH, Mansell M. The use of povidone iodine in exit site care for patients undergoing continuous peritoneal dialysis (CAPD). *J Hosp Infect* 1997;**35**:287–93.

Wong, 2002
Wong FSY, Chan W-K, Chow N-Y, Tsui Y-T, Yung JCU, Cheng Y-L. Comparison of exit-site infection with the use of pure liquid soap and chlorhexidine soap in daily exit-site care. *Hong Kong J Nephrol* 2002;**4**:54–9.

Wong, 2003
Wong SSH, Chu K-H, Cheuk A, Tsang WK, Fung SKS, Chan HWH, *et al*. Prophylaxis against Gram-positive organisms causing exit-site infection and peritonitis in continuous ambulatory peritoneal dialysis patients by applying mupirocin ointment at the catheter exit site. *Perit Dial Int* 2003;**23**(Suppl 2):S153–8.

Zimmerman, 1991
Zimmerman SW, Ahrens E, Johnson CA, Craig W, Leggett J, O'Brien M, *et al*. Randomized controlled trial of prophylactic rifampin for peritoneal dialysis-related infections. *Am J Kidney Dis* 1991;**18**:225–31.

Appendix 5

Detailed quality assessment results for included trials

Study ID	Allocation concealment	Blinding of investigators	Blinding of participants	Blinding of assessor	Blinding of data analysis	ITT	Lost to follow-up
Bennett-Jones, 1988[35]	Inadequate	Unclear	Unclear	Unclear	Unclear	Not stated	Yes
Bernardini, 1996[40]	Unclear	Unclear	Unclear	Unclear	Unclear	Stated	Unclear
Bernardini, 2005[41,42]	Adequate	Yes	Yes	Unclear	Unclear	Stated	Unclear
Blowey, 1994[54]	Unclear	Unclear	Unclear	Unclear	Unclear	Not stated	Unclear
Cavdar, 2004[43]	Unclear	Unclear	Unclear	Unclear	Unclear	Not stated	Unclear
Fuchs, 1990[50]	Unclear	Unclear	Unclear	Unclear	Unclear	Not stated	Yes
Gadallah, 2000[44,45]	Inadequate	Unclear	Unclear	Unclear	Unclear	Not stated	Unclear
Luzar, 1990[3]	Unclear	Unclear	Unclear	Unclear	Unclear	Not stated	Yes
Lye, 1992[36]	Inadequate	Unclear	Unclear	Unclear	Unclear	Not stated	Unclear
Mupirocin Study Group, 1996[55,56]	Unclear	Unclear	Unclear	Unclear	Unclear	Stated	Unclear
Perez-Fontan, 1992[57]	Unclear	Unclear	Unclear	Unclear	Unclear	Not stated	Yes
Poole-Warren, 1991[51]	Unclear	Unclear	Yes	Unclear	Unclear	Not stated	Unclear
Sesso, 1988[47]	Unclear	Unclear	Unclear	Unclear	Unclear	Not stated	Yes
Sesso, 1994[58]	Unclear	Unclear	Unclear	Unclear	Unclear	Not stated	Yes
Sharma, 1971[37]	Unclear	Unclear	Unclear	Unclear	Unclear	Not stated	Yes
Turner, 1992[52]	Unclear	No	No	No	Unclear	Not stated	Unclear
Waite, 1997[46]	Unclear	Unclear	Unclear	Yes	Unclear	Not stated	Yes
Warady, 2003[53]	Unclear	No	No	Unclear	Unclear	Not stated	Yes
Wilson, 1997[48]	Unclear	Unclear	Unclear	Unclear	Unclear	Not stated	Yes
Wong, 2002[49]	Inadequate	Unclear	Unclear	Unclear	Unclear	Not stated	Yes
Wong, 2003[38]	Unclear	No	No	Unclear	Unclear	Not stated	Yes
Zimmerman, 1991[39]	Unclear	No	No	No	No	Not stated	Unclear

Appendix 6

Detailed description of included studies

Study	Study details	Intervention/comparator	Intervention 1 population characteristics	Intervention 2 population characteristics	Intervention 3 population characteristics
Bennett-Jones, 1988[35]	Single-centre RCT 27 participants Follow-up = 28 days Full text	Gentamicin 1.5 mg/kg body weight given i.v. by anaesthestist at time of induction of anaesthesia in anaesthetic room (n = 13) versus no treatment (n = 13; 1 withdrawn)	Age mean ± SD 52.7 ± 18.6 years 8 male/5 female	Age mean ± SD 53.1 ± 13.0 years 9 male/4 female	
Bernardini, 1996[40]	Single-centre RCT 82 participants Follow-up = mean 1 year Full text	Mupirocin calcium ointment 2%, applied daily to catheter exit site (n = 41) versus 300 mg oral rifampin twice per day for 5 days once every 3 months (n = 41)	49% male/51% female 41/41 adult Time on PD mean (range) 1.3 ± 1.8 (0–57) years 44% *S. aureus* carriage	59% male/41% female 41/41 adult Time on PD mean (range) 1.1 ± 1.7 (0–9.1) years 44% *S. aureus* carriage	
Bernardini, 2005[41,42]	Multicentre RCT 133 participants Follow-up = median (range) 8 (0.13–28.2) months Full text	Mupirocin 2% cream daily to catheter exit site (n = 66) versus gentamicin cream 0.1% daily to exit site (n = 67)	Age mean ± SD 51 ± 15 years 38 male/28 female 66/66 adult 9/66 *S. aureus* carriage	Age mean ± SD 54 ± 15 years 34 male/33 female 67/67 adult 9/67 *S. aureus* carriage	
Blowey, 1994[54]	Single-centre RCT 15 participants Follow-up = 1 month Full text	Oral rifampin (20 mg/kg/day in 2 doses for 5 days) and bacitracin (topical to anterior nares 2 times per day for 7 days) (n = 7) versus no treatment (n = 8)	7/7 *S. aureus* carriage	8/8 *S. aureus* carriage	
Cavdar, 2004[43]	Single-centre RCT 36 participants Follow-up = 6 months Full text	Mupirocin to exit site once weekly (n = 18) versus mupirocin to exit site 3 times weekly (n = 18)	Age mean 55.3 ± 1.8 years 10 male/8 female 3/18 *S. aureus* carriage	Age mean 55.0 ± 2.3 years 11 male/7 female 0/18 *S. aureus* carriage	

continued

Study	Study details	Intervention/comparator	Intervention 1 population characteristics	Intervention 2 population characteristics	Intervention 3 population characteristics
Fuchs, 1990[50]	RCT 51 participants Follow-up = mean (range) 6.63 (1–12) months Full text	Washing exit site with chlorhexidine, then rinsing well, no dressing applied (n = 18), versus cleaning the exit site once daily with 0.005% sodium hypochlorite no dressing applied (n = 13), versus daily cleansing of exit site with 10% povidone–iodine swabsticks, followed by application of povidone ointment and a dry sterile dressing (n = 20)	Age mean 46 years 7 male/11 female 66/66 adult Time on PD mean ± SD 14.3 ± 12.9 months	Age mean 47 years 7 male/6 female 67/67 adult Time on PD mean ± SD 21.2 ± 28.6 months	Age mean 55 years 13 male/7 female 67/67 adult Time on PD mean ± SD 23.6 ± 19.0 months
Gadallah, 2000[44,45]	Quasi-RCT 265 participants (305 catheters) Follow-up = 14 days Full text	I.v. vancomycin 1000 mg ~12 hours before PD catheter placement (n = 90; 103 catheters) versus i.v. cefazolin 1000 mg ~3 hours before PD catheter placement (n = 88, 102 catheters) versus no antibiotics for at least 1 week before procedure (n = 87, 100 catheters)	Age 46 (15–72) years 38 male/52 female 90/90 adult 32/90 diabetic nephropathy 42/90 hypertension and renovascular disease 4/90 glomerulonephritis 3/90 APKD 4/90 lupus nephritis 5/90 HIV nephropathy	Age 47 (20–81) years 43 male/45 female 88/88 adult 30/88 diabetic nephropathy 38/88 hypertension and renovascular disease 5/88 glomerulonephritis 4/88 APKD 4/88 lupus nephritis 7/88 HIV nephropathy	Age 45 (19–76) years 38 male/49 female 87/87 adult 28/87 diabetic nephropathy 41/87 hypertension and renovascular disease 6/87 glomerulonephritis 2/87 APKD 5/87 lupus nephritis 5/87 HIV nephropathy
Luzar, 1990[3]	Multicentre RCT 127 participants Follow-up = mean 9.03 months Full text	Povidone–iodine (concentration 20 g/l) applied to exit site with sterile gauze) (n = 74) versus cleaning of exit site daily with non-disinfectant soap on sterile gauze (simple soap in UK or savon de Marseilles in France) (n = 53)	63% male/37% female 74/74 adult 17% diabetic glomerulonephritis	59% male/41% female 53/53 adult 11% diabetic glomerulonephritis	

continued

Study	Study details	Intervention/comparator	Intervention 1 population characteristics	Intervention 2 population characteristics	Intervention 3 population characteristics
Lye, 1992[36]	Single-centre quasi-RCT 50 participants Follow-up = 3 months Full text	Preoperative antibiotics: cefazolin (500 mg) and gentamicin (80 mg) as rapid i.v. infusion no more than 60 minutes before surgery (n = 25) versus no treatment (n = 25)	Age mean ± SD 56.0 ± 14.3 years 8 male/17 female 17/25 diabetic nephropathy 4/25 glomerulonephritis 1/25 urolithiasis 3/25 other 3/25 *S. aureus* carriage 6/25 MRSA	Age mean ± SD 52.3 ± 14.0 years 15 male/10 female 13/25 diabetic nephropathy 7/25 glomerulonephritis 1/25 urolithiasis 4/25 other 6/25 *S. aureus* carriage 4/25 MRSA	
Mupirocin Study Group, 1996[55,56]	Multicentre RCT 267 participants Follow-up = max. 18 months Full text	Calcium mupirocin 2%, 2 × daily for 5 consecutive days every 4 weeks (n = 134) versus placebo ointment (n = 133)	Age mean 60.3 years 60.4% male/39.6% female 16.4% hypertension and renovascular disease 26.1% glomerulonephritis 10.4% polycystic disease 5.2% pyelonephritis 24.6% other 134/134 *S. aureus* carriage	Age mean 60.3 years 60.2% male/39.8% female 8.3% hypertension and renovascular disease 19.5% glomerulonephritis 5.3% polycystic disease 7.5% pyelonephritis 36.8% other 133/133 *S. aureus* carriage	
Perez-Fontan, 1992[57]	Single-centre RCT 22 participants Follow-up = mean (range) 9.5 (3–15) months Full text	2% mupirocin nasal ointment t.d.s. for 7 days (n = 12) versus 0.1% neomycin sulphate ointment t.d.s. for 7 days (n = 10)	Age mean ± SD 51 ± 15 years 5 male/7 female Time on PD 32 ± 16 months 12/12 *S. aureus* carriage	Age mean ± SD 48 ± 21 years 5 male/5 female Time on PD 32 ± 15 months 10/10 *S. aureus* carriage	
Poole-Warren, 1991[51]	Multicentre RCT 124 participants Follow-up = 1 year Full text	Vaccinated with combined staphylococcus toxoid/whole killed staphylococci formulation (SB). Given i.m. Six injections given in increasing concentrations (1, 5, 10, 20, 50% and undiluted) over 6 weeks. Four booster injections (each 1 ml of undiluted SB) given every 12 weeks (weeks 17, 29, 41 and 53) (n = 65), versus placebo (normal saline injections given i.m. on same schedule) (n = 59)	Age mean ± SD 54 ± 11 years 1.5 [ratio] 12/65 diabetic nephropathy 11/65 hypertension and renovascular disease 16/65 glomerulonephritis 5/65 reflux nephropathy 7/65 analgesic nephropathy 8/65 other Time on PD mean ± SD 1.5 ± 1.3 years 13/40 *S. aureus* carriage	Age mean ± SD 52 ± 14 years 0.7 [ratio] 9/59 diabetic nephropathy 5/59 hypertension and renovascular disease 18/59 glomerulonephritis 2/59 reflux nephropathy 9/59 analgesic nephropathy 6/59 other Time on PD mean ± SD 1.7 ± 1.9 years 11/36 *S. aureus* carriage	

continued

Study	Study details	Intervention/comparator	Intervention 1 population characteristics	Intervention 2 population characteristics	Intervention 3 population characteristics
Sesso, 1988[47]	RCT 39 participants Follow-up = Group A 150 patient months; Group B 133 patient months Correspondence	4% chlorhexidine gluconate (n = 20) versus neutral soap (n = 19)			
Sesso, 1994[58]	Single-centre RCT 31 participants Follow-up = mean ± SE 7.8 ± 0.6 months Full text	2% sodium fusidate (ointment as applied to anterior nares and catheter exit site × 2 daily for 5 days) (n = 9) versus 200 mg ofloxacin orally every 48 hours for 5 days (n = 9) versus placebo tablets (n = 13)	Age mean ± SE 46.1 ± 3.8 (33–69) years 6 male/3 female 9/9 adult 1/9 diabetic nephropathy 0/9 glomerulonephritis 8/9 other Time on PD mean ± SE 9.9 ± 4.0 months *S. aureus* carriage: all = 9/9; nares = 2/9; exit site = 2/9; nares + exit site = 5/9	Age mean ± SE 36.6 ± 4.6 (22–61) years 6 male/3 female 9/9 adult 3/9 diabetic nephropathy 1/9 glomerulonephritis 5/9 other Time on PD mean ± SE 16.1 ± 6.2 months *S. aureus* carriage: all = 9/9; nares = 0/9; exit site = 4/9; nares + exit site = 5/9	Age mean ± SE 42.1 ± 4.6 (17–68) years 9 male/4 female 13/13 adult 1/13 diabetic nephropathy 3/13 glomerulonephritis 6/13 other Time on PD mean ± SE 15.0 ± 4.5 months *S. aureus* carriage: all = 13/13; nares = 4/9; exit site = 4/13; nares + exit site = 5/13
Sharma, 1971[37]	RCT 41 participants (95 dialysates) Follow-up = at least 48 hours Full text	Neomycin (0.5 g by mouth or nasogastric tube every 6 hours) (n = 48 dialysates) versus placebo (n = 41 dialysates)			
Turner, 1992[52]	Single-centre RCT 66 participants Follow-up = mean (range) 20 ± 17 (2–49) versus 21 ± 17 (2–54) versus 23 ± 20 (1–60) weeks Full text	Immobiliser (n = 22) versus tape (n = 23) versus non-immobilised (n = 21)	Age mean ± SD 45 ± 15.51 years 10/22 *S. aureus* carriage	Age mean ± SD 40 ± 14.26 years 11/23 *S. aureus* carriage	Age mean ± SD 43 ± 15.8 years 6/21 *S. aureus* carriage

continued

Study	Study details	Intervention/comparator	Intervention 1 population characteristics	Intervention 2 population characteristics	Intervention 3 population characteristics
Waite, 1997[46]	Single-centre RCT 120 participants (117 analysed) Follow-up = mean 14.6 vs 13.2 months Full text	3.5 g 10% povidone–iodine ointment (n = 61) versus no intervention (n = 56)	Age mean ± SD 54.4 ± 15.1 years 33 male/28 female 22/61 *S. aureus* carriage	Age mean ± SD 53.2 ± 14.5 years 30 male/26 female 14/56 *S. aureus* carriage	
Warady, 2003[53]	Multicentre RCT 121 participants Follow-up = mean 305.3 ± 22.2 vs 313.0 ± 26.5 days Abstract	'Flush before fill' flushing of 100 ml of sterile dialysate from each bag of dialysate through the cycler tubing and into the drain bag following drainage of effluent from the patient and before the infusion of sterile dialysate into the patient (n = 62) versus 15 ml of sterile dialysate flushed through the tubing originating only from the heater bag into the drain bag prior to infusion (n = 59)	Age mean 11.4 ± 5.6 years 54.8% male/45.2% female 62/62 paediatrics 3.2% reflux nephropathy 41.9% other Time on PD 24.6(3.8) months	Age mean 11.2 ± 6.0 year 59.3% male/40.7% female 59/59 paediatrics 1.7% reflux nephropathy 50.8% other Time on PD 18.9 (2.9) months	
Wilson, 1997[48]	RCT 130 participants (149 catheters) Follow-up = 1 year or until a significant difference was present Full text	Sterile povidone iodine (2.5%) dry powder spray to exit site every time dressing changed (every other day) (n = 77 catheters) versus no intervention (n = 72 catheters)	Age mean (range) 53 (18–82) years 55 male/22 female 77/77 adults 3.2% reflux nephropathy 41.9% other Time on PD median (range) 422 (52–1280) days	Age mean (range) 51 (21–76) years 43 male/29 female 72 adults 1.7% reflux nephropathy 50.8% other Time on PD median (range) 512 (42–1572) days	
Wong, 2002[49]	Single-centre quasi-RCT 124 participants (117 analysed) Follow-up = 6 months Full text	4% chlorhexidine liquid soap used in cleansing of exit site (n = 69) versus pure liquid soap used in cleansing of exit site (n = 48)	Age mean 59.0 ± 11.50 years 34 male/35 female	Age mean 56.3 ± 11.7 years 23 male/25 female	

continued

Study	Study details	Intervention/comparator	Intervention 1 population characteristics	Intervention 2 population characteristics	Intervention 3 population characteristics
Wong, 2003[38]	Single-centre RCT 166 participants (154 analysed) Follow-up = 5 months Full text	Mupirocin applied using cotton-tipped applicator to apply ointment round skin around catheter exit site daily (n = 78, 73 analysed) versus no intervention (n = 88, 81 analysed)	Age mean 60 ± 12 years 32 male/41 female Time on PD 41 ± 37 months 16/73 *S. aureus* carriage	Age mean 59 ± 13 years 47 male/34 female Time on PD 39 ± 25 months 14/81 *S. aureus* carriage	
Zimmerman, 1991[39]	Single-centre RCT 64 participants Follow-up = mean ± SEM 10.2 ± 1.2 vs 12.0 ± 1.3 months Full text	Rifampin 300 mg 2 times daily for 5 days at the start of each 12-week interval (n = 32) versus no treatment (n = 32)	Age mean ± SEM 53 ± 3 years 17 male/15 female 32/32 adults Time on PD 41 ± 37 months 9/32 *S. aureus* carriage	Age mean ± SEM 55 ± 4 years 24 male/8 female 32/32 adults Time on PD 39 ± 25 months 8/32 *S. aureus* carriage	

APKD, adult polycystic kidney disease; SD, standard deviation; SE, standard error; SEM, standard error of the mean.

Appendix 7

Proposed methods for parameterising the economic model

Probabilities

As mentioned before, the main source of effectiveness data that would be used to populate the model is the review of effectiveness (Chapter 3). However, as described below, other sources such as existing datasets and population cohort studies may be required. The outcomes of the systematic review of effectiveness were primarily presented in terms of relative effect sizes (RRs) for the comparison of prophylactic antibiotic with no treatments. By identifying the relevant transition probabilities for the 'no treatment' intervention and combining with relevant relative effect sizes for the prophylactic antibiotic intervention, the transition probabilities for this intervention can be derived.

Estimation of baselines comparator transition probabilities

One source of data on the relevant transition probabilities for this is the control arms of studies that compared an active treatment with no treatment. *Table 13* describes the parameters used to determine transitions between the states of the model. The data that might be used for these parameters are described below.

Transition probabilities from 'Catheter insertion'

Following the initial insertion of the PD catheter a person would receive PD, although they may have a risk of being a carrier of *S. aureus*. Ideally, the risk of *S. aureus* carriage would come from a large population based survey of patients pre-dialysis. Some data on the risk of *S. aureus* carriage at the time of catheter insertion could be obtained from systematic review of effectiveness[36,46] (see *Table 6*). These sources provide rates of *S. aureus* carriage of between 18.0 and 30.8% and a crude mean of 27.0% (46 cases out of 167 trial participants). In the model, it would be assumed that 27% of those who do not die less those who experience an infection (see below) would transfer into the state of 'On PD with SA carriage'.

The risk of infections caused by *S. aureus* following catheter insertion could also be provided by review of effectiveness data. The systematic review of effectiveness sought to identify the number of patients with peritonitis, peritonitis rates, peritonitis relapses, exit-site and tunnel infection rates. Although the aim was to identify exit-site, tunnel and peritonitis infections separately, most of the studies reported exit-site/tunnel infections together (Chapter 3). *Table 6* provides details on the number of patients without *S. aureus* carriage who develop peritonitis and also the mean number of episodes per patient year. The data from the no treatment arms of these studies can

TABLE 13 *Baseline parameter values required for the model*

State	Parameter
'Catheter insertion'	On PD without SA carriage On PD with SA carriage On PD with an infection
'On PD without SA'	Remain on PD without SA carriage On PD with SA carriage On PD with an infection Transfer to HD Die
'On PD with SA'	Go back to PD without SA carriage Remain on PD with SA carriage On PD with an infection Transfer to HD Die
'Infection'[a]	Infection cured, return to PD without SA carriage Relapsing infection Temporary HD HD Die
'Temporary HD'	Infection cured, return to PD without SA carriage HD Die
'Permanent HD'	Remain on HD Die

[a] In the hypothetical model, 'infection' is defined as a single state. In a full model, the different types of infection might be defined as individual states that would allow them to occur either singularly or in sequence.

be used to provide some information of the risks of infection (and types of infection) per year. However, very few data are available.[39] A crude estimate of the risk of peritonitis per patient per month would be 1.3%. A similar estimate for the risk of exit-site or tunnel infections would be 5.4%. Such data come from a small study and hence are imprecise and unreliable.[39] Ideally, such data would be replaced by data from a larger study. Data are also required on the risk of infections for those with *S. aureus* carriage. Data from the no treatment arms for comparisons of alternative methods to treat *S. aureus* carriage provided by the systematic review are one source of data[55] (*Table 8*). However, such data are not comparable to the risks of infections for those without *S. aureus* carriage. For example, from the data available, the risk of peritonitis per patient per month can be calculated as 1.9% and the risk of exit-site and tunnel infections as 3.6%. It might be expected that the infections caused by *S. aureus* would be greater in the group that were known carriers of *S. aureus*. Ideally, the information on infection rates amongst those who are and are not carriers of *S. aureus* would come from a single study of sufficient size to provide reasonably precise and reliable data for a UK setting.

Survival rates or death rates for patients on PD would also be needed. The Renal Registry has published survival rates derived from data on 3-year survival rates using Kaplan–Meier survival analysis.[1] To use such data would require that the proportion of people dying from *S. aureus* infection while on PD is only a small proportion of the total risk of death on PD.

Transition probabilities from 'On PD without SA carriage'

Patients who are *S. aureus* free can remain on PD until they die either free of *S. aureus* carriage or become carriers of *S. aureus*. These is insufficient information on the risk that a patient might develop *S. aureus* carriage from the review of effectiveness, but one study reported how the risk of *S. aureus* nasal carriage changes over time.[51] This study is small and even though such data could be used in the model, they are likely be both imprecise and unreliable. Ideally, such data should come from the control arm of a large RCT or from a large cohort study relevant to a UK setting.

As indicated in *Table 10*, a patient on PD but free of *S. aureus* also faces the probability of developing an infection or dying. The data required to derive the relevant transition probabilities could be derived using similar methods to those outlined for the transitions from 'Catheter insertion'.

The remaining transition probability required from the state 'On PD without SA carriage' is the transition to HD. The review of effectiveness sought to establish the number of patients requiring catheter replacement/removal (and hence requiring temporary HD, a clinically possible transition but not one allowed for this state in this hypothetical model) and the number of patients permanently switching to HD (unclear whether this included both permanent and temporary transfers). Although some data were reported on catheter removal for those with *S. aureus* carriage (see *Table 6*), no data were identified on the number of patients switching modality. A search of the Renal Registry indicated that the sequential annual risk of switching from PD to HD permanently was 11% at the end of the first year, 18% at the end of the second year and 23% at the end of the third year (based on data for patients established on PD in 1998–9, the most recent years for which data are available).[1] From such data, monthly transition probabilities might be estimated.

Transition probabilities from 'On PD with SA carriage'

Similar methods and data sources would be required to estimate the transition probabilities from this state as those described for transitions from 'Catheter insertion' and 'On PD without SA carriage'.

Transition probabilities from 'Infection'

Ideally, the likelihood that an infection is cured would be derived by consideration of the data on the effectiveness of interventions to treat *S. aureus* interventions. The most appropriate source of such data would not be the review of effectiveness reported in Chapter 3 but a new review of studies looking at alternative treatments of infections (the data from such a review are presented in Appendix 8). From such a review, data would be extracted on the likelihood of infections that do not resolve and the risk of death or transferring modality. Following consultation with the clinical co-reviewers, it has been assumed in the model that should a patient suffer three consecutive months (cycles) of infection that they would automatically transfer to the state of temporary HD.

Transition probabilities from 'Temporary HD'

Patients who enter this state will remain in it for only one cycle; at the end of that cycle, they may

either transfer to the state 'On PD without SA carriage', transfer to the state of 'Permanent HD' or die. The risk of death is not likely to be greatly different to the rates used for earlier states. However, there is no evidence available on the likelihood of returning to PD or moving to permanent HD. Data from the Renal Registry suggest that patients rarely switch from HD to PD (approximately 3% per annum), but these numbers may not be applicable for the group of patients who switch to HD only until their symptoms resolve. Ideally, data from a well-designed study would be useful but, as this is only a transitory state, sensitivity analysis could be conducted over a range of plausible values.

Transitions from 'Permanent HD'

In the model, it is assumed that once patients are transferred to HD they will stay in this state until they die. The Renal Registry has published survival rates using Kaplan–Meier survival analysis and these data could be used to establish the relevant transition probabilities.

Estimation of relative effect sizes

Data on relative effect sizes for an active treatment compared with no treatment (e.g. antibiotics versus no antibiotics for the prevention of carriage) can, when combined with the transition probabilities for no treatment, be used to estimate the transition probabilities for the an active treatment, e.g. prophylactic antibiotics. The various relative effect sizes estimated as part of the review of effectiveness are presented in *Figures 1–7*. Although such relative effect sizes could be used in a model, they are limited as they are based on sparse data, and a full evaluation comparing all relevant interventions would rely on indirect comparisons. Details of the data available for comparison of antibiotics provided at the time of catheter insertion compared with no treatment are provided below.

S. aureus carriage cure rates

This relative effect size is needed to estimate the probability of entering 'PD without SA carriage' and 'PD with SA carriage' states following prophylactic use of antibiotics at the time of catheter insertion. From the review of effectiveness, no data were available on the ability of prophylactic antibiotics at the time of catheter insertion to prevent infection with *S. aureus*. Some estimate could be obtained by considering the effectiveness of antibiotics at curing those with known *S. aureus* carriage. *Table 8* reports the results on the number of people treated for *S. aureus* carriage during dialysis. The number of patients cured (those who did not have *S. aureus* at the end of the treatment) could therefore be derived from these data.

S. aureus infection rates

These relative effect sizes would be used to estimate the likelihood of developing an infection. Data are not available split by whether the infections occurred in those who were *S. aureus* carriers and those who were not. Although consideration of data provided in *Figures 1*, *2*, *5* and *6* might provide some information with which plausible estimates could be derived. Nevertheless, ideally such data would be more usefully derived from the participant-level data from a large controlled study.

Exit site/tunnel and peritonitis cure rates

Once an infection has occurred, the assumption would be made that the probability of cure would be independent of the intervention used to prevent or treat *S. aureus* carriage. Thus, the transition probabilities from the state of 'Infection' following the use of prophylactic antibiotics would be the same as those following no treatment. What would vary between the two interventions would be the probability of an infection.

Modality changes

Few studies provided any data on the number of patients switching modality from PD or the number of patients requiring catheter removal (and at least a move to temporary HD). The studies identified in Chapter 3 were not designed to provide such data and provided, at best, only proxy indicators. Such data as are available are presented in *Tables 6* and *8* but are both imprecise and potentially unreliable due to the small size of the studies. Furthermore, such data would ideally be split by those who were *S. aureus* carriers and those who were not carriers. Ideally, such data would be more usefully derived from the participant-level data from a large controlled study.

Relative effect sizes for the risk of modality changes from the states of 'Infection', 'Temporary HD' and 'Permanent HD' would not be required as these transition probabilities are assumed to be independent of the method used to prevent or treat *S. aureus* carriage.

Death or survival rates

Exactly the same situation arises for relative effect sizes associated with the risk of death as those

noted above for changes in modality. Again, data from a large controlled study would be useful. Such a study would need to have sufficiently long enough follow-up to capture differences in survival (and other relevant effects).

Cost data

The perspective of the assessment of costs would be that of the NHS and Personal Social Services. Resource use data would be identified from published studies, healthcare service utilisation data and advice from experts in this field. Cost data used to illustrate this part of the hypothetical model were mainly extracted from the literature published in 1999 and were inflated to 2005 using the Hospital and Community Health Services (HCHS) pay and price inflation indices[72] and the currency used is pounds sterling (£). The main cost components were the costs of the interventions themselves and the costs of treating an infection or the consequences of an infection (e.g. a change in modality or the replacement of a catheter). Details of the cost values used are reported in *Table 14* and the methods used to derive these values are described below.

Estimation of the cost of catheter insertion

The cost of inserting a peritoneal catheter was derived from Kirby and Vale.[73] These costs were calculated by identifying items of resource use from studies and by consulting the renal administrator at NHS Grampian. Local prices were then attached to each item and drug costs obtained from nationally available sources. The cost of access was estimated at £1955 in 1999 (£2235 in 2004 prices). The same cost would be used for patients who required a replacement of a PD catheter (following a period on temporary HD).

Estimation of the cost of interventions to prevent or treat *S. aureus* carriage

Data on patients who received antibiotics were derived from a published study.[59] The cost data reported were based on the consideration of the unit dose, route of administration, doses per day and duration of therapy. The total cost of 1 year's treatment per identified carrier of *S. aureus* was £157 (at 1994 prices) and this comprised costs of £64 for screening and £93 for antibiotics. These costs were based on one antibiotic (mupirocin). The inflated annual cost per identified carrier of *S. aureus* is £179 (£73 for screening and £106 for antibiotic).

Estimation of the costs of treating infections

Data on patients who received antibiotics were derived from a published study[59] and the costs of treatment were comprised of unit dose, route of administration, doses per day and duration. The study indicated that the mean costs of treating infections were highly skewed. The mean costs of treating all infections (exit-site infections and other infections) was £178 for the prophylaxis group and £379 for the placebo group at 1994 prices. The difference between the means was not statistically significant –£201 (–£493 to £90). The cost data inflated to 2005 prices were £203 for the prophylaxis group and £433 for the placebo group.

Estimation of the costs of providing dialysis

The cost data for these interventions included consumables such as catheters and prophylactic treatments, staff costs, capital costs of providing HD, overheads and transport where necessary. These data were based on data provided by the EURODICE study (Wordsworth S, Health Economist, Oxford: personal communication, 2005). This study was an observational study investigating the costs, effects and cost-effectiveness of PD and HD in 10 European centres, two of which were in the UK. Costs in each centre were detailed data on the use of resources required for the different dialysis modalities in use. These were collected between 1999 and 2001 during site visits, detailed examination of records and the completion of questionnaires by manager, healthcare professionals and patients. In this review, data from the two UK centres (Aberdeen and Dundee) would be used as they are most likely to be applicable to the UK. The five main categories included in the estimation of costs were consumables, staff, capital, overheads and patient transport. The consumables were composed mainly of disposable items such as dialysers, line and recombinant human erythropoietin (EPO). Staff costs were based on weekly work rosters from the units which detailed the time devoted to the provision of HD and PD. The capital costs for HD were composed of building costs, dialysis machine, repairs, water treatment and computers. Although PD typically takes place outwith the hospital, some hospital costs would normally be incurred. The capital costs of PD were based on building costs, weighing scales, bag warmers, drip stand and blood pressure monitor. Staff costs were derived by identifying the salary grades of those who spent time with the patients (both medical and nursing)

and the amount of time they spent with the patients. Overhead costs included floor space allocation that was composed of cleaning, building, engineering, local government authority taxation on buildings (rates), water, energy and occupied bed days allocation that were composed of medical records, linen and catering. The total cost of HD for 1 month was £2458 and for PD £1603 at 2005 prices.

Estimation of costs of change in modality

One of the main effects of infections is the need to remove and replace the catheter and the cost of change in modality of treatment. The cost of loss of catheter/catheter replacement is based on the cost of a catheter, which is £2235 as reported above. The cost of switch in modality is the cost of HD, including creation of the access fistula. These data were also derived from Kirby and Vale and were estimated using the same methods as described for the cost of catheter insertion.[73] The cost was £1959 (1999 prices), which was inflated to £2240 (2005 prices).

Estimation of quality of life

The main measure of effectiveness that would be used within the economic evaluation is QALYs. QALYs would be estimated by multiplying the length of time spent in each health state by a quality of life weight (a utility value) for that state. A search for studies on quality of life identified one study.[74] The data came from 165 dialysis patients and were elicited using the EQ-5D instrument. Their results indicated that patients undergoing hospital HD had a utility score of 0.66, satellite HD patients had a value of 0.81, continuous ambulatory PD patients had a value of 0.71 and continuous cycling PD patients had a value of 0.81. As these do not come from an RCT, these utility scores are influenced by the choice of modality for each patient (i.e. there may be a selection bias). Although the utility scores for patients with end-stage renal disease were identified, there were no data on utilities of people on dialysis with infections.

Another further source of utility values was the data collected by the European Dialysis and Cost Effectiveness (EURODICE) study. This study prospectively identified cohorts of patients starting on HD and PD and collected EQ-5D data from patients on 1 July 1998 and 31 October 1999 every 6 months for a period of 2–3 years. Health state utilities were collected from all study participants including those from two UK centres (Aberdeen and Dundee). These data had not been previously reported but were obtained from the study researchers (Caskey F, Consultant Nephrologist, Bristol: personal communication, 2005)[75,76] and the utilities were derived using the UK population tariffs.[77]

The modality of first treatment was assumed to be the method the patient was receiving at 90 days and not the initial dialysis method, as many patients, especially those being referred late to renal units, undergo a brief period of HD before being established on PD. Utility scores for this and three other time points (collected every 6 months) were estimated from the data provided. Secondary analysis was also carried out on the scores of patients who transferred from PD to HD. However, the numbers of patients changing treatment modality from PD to HD were very low, so the estimates were not reliable. Although there is not much detail on what type of HD and PD was being administered by the 12th month, EQ-5D values are similar to these reported by de Wit and colleagues.[74] The utility value for patients receiving PD was 0.84 and for those receiving HD it was 0.69. These scores could therefore be used as the utility scores associated with 'PD without SA carriage', 'PD with SA carriage', 'Temporary HD',

TABLE 14 *Cost parameters available for use in the hypothetical model*

Cost element	Value (£)	Unit
Peritoneal dialysis	1603	Cost per month
Permanent and temporary haemodialysis	2458	Cost per month
Prophylaxis for *S. aureus* carriage	15	Cost
Treatment for *S. aureus* carriage	15	Cost per course
Treatment of exit-site infection	192	Cost per treatment
Treatment of tunnel infection	1035	Cost per treatment complication; may require removal of catheter
Catheter replacement	2235	Cost per procedure
Cost of creating access for haemodialysis	2240	Cost per access
Treatment of peritonitis	203	Cost per treatment

and 'Permanent HD' in the model, as they are more representative of the UK population than those available from de Wit and colleagues.[74] These data, however, should be treated with great caution as they are associated with considerable imprecision (which, although reported here, would need to be incorporated into the economic evaluation) derived from a non-randomised study and, like the data from de Wit and colleagues,[74] will suffer from patient selection bias.

The EURODICE data provided no information with which to inform estimates of the utility associated with infections. Ideally, primary data collection would be performed to inform this. In the absence of such data, one approach would be to perform a sensitivity analysis using a range of values to explore the impact of this uncertainty on the results. A second approach would be to explore the use of other data sets such as the Health Outcomes Data Repository (eHODAR) (http://www.crc-limited.co.uk), although it is unlikely that such sources will contain sufficient information on the utilities relevant to this study.

Appendix 8

Treatment of clinical infections

Eight trials evaluated different antibiotic regimes for the treatment of PD-related infections and one trial compared intraperitoneal urokinase with a placebo.

Table 15 provides details, where reported, of the results for the following outcomes: number of patients with peritonitis caused by *S. aureus*; number of patients to have a primary response or successful treatment; number of patients for whom the treatment has failed; peritonitis relapse (number and specify time to) caused by *S. aureus*; and number of patients requiring catheter removal.

Number of patients with exit-site and/or tunnel infections caused by *S. aureus*

Plum and colleagues[78] reported the number of exit sites with *S. aureus* carriage as 6/8 versus 4/8; tunnel erythema before treatment 2/6 versus 1/4 and after treatment 0/6 versus 0/4; and tunnel drainage before treatment 6/6 versus 4/4 and after treatment 2/6 versus 1/4.

Side-effects

One trial[79] reported one pseudo-obstruction and one hypotension as a result of antibiotic use in the intraperitoneal vancomycin plus gentamicin group and three nausea and one abdominal swelling in the oral ciproflaxin group.

Death due to peritonitis caused by *S. aureus*

Tong and colleagues[86] reported that one death in the placebo group was due to peritonitis.

No data were reported for the following outcomes: number of patients requiring catheter replacement caused by *S. aureus*; number of patients switching to HD; hospitalisation rates; quality of life; and development of antibiotic resistance.

TABLE 15 *Outcome results for studies assessing treatment of clinical infections*

Study	Comparison	*S. aureus* peritonitis (no.)	Primary response/ treatment success (no.)	Treatment failure (no.)	Peritonitis relapse (no.)	Catheter removal (no.)
Antibiotic vs antibiotic						
Bennett-Jones, 1990[79]	I.p. vancomycin + gentamicin	5/26	2/5	3/5	1/5 (14 days)	–
	Oral ciproflaxin	5/22	4/5	1/5	1/5 (14 days)	–
Cheng, 1991[80]	Oral ofloxacin	3/23[a]	3/3	0/3	0/3	–
	I.p. vancomycin/aztreonam	5/25[a]	5/5	0/5	1/5	–
Flanigan, 1991[81]	I.p. vancomycin	–	–	–	–	4/30
	I.p. cefazolin	–	–	–	–	5/15
Gucek, 1994[82]	I.p. cefazolin	15%	1/3	2/3	–	–
	Oral ofloxacin	0%	–	–	–	–
Gucek, 1997[83]	Cefazolin/netilmycin	3/26[a]	2/3	1/3	–	–
	Vancomycin/ceftazidime	2/26[a]	2/2	0/2	–	–
Leung, 2004[84]	I.p. imipenem/cilastatin	2/51	0/2	–	–	–
	I.p. cefazolin/ceftazidime	13/51	4/13	–	–	–
Merchant, 1992[85]	I.p. imipenem/cilastatin	2/21	1/2	1/2	–	1/2
	I.p. netilmicin/vancomycin	1/20	1/1	0/1	–	0/1
Plum, 1997[78]	Oral clindamycin	–	–	–	–	–
	I.p. clindamycin	–	–	–	–	–
Other						
Tong, 2005[86]	I.p. urokinase	7/44 (3 MRSA)	3/4	–	–	–
	Placebo	11/44 (4 MRSA)	3/7	–	–	–

[a] Episodes.

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