

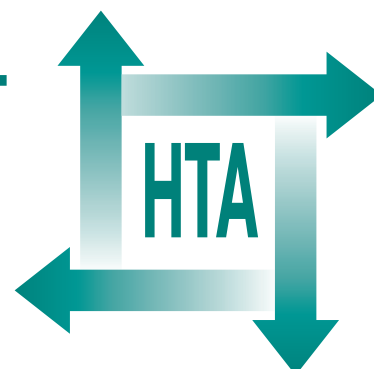
# **A systematic review and economic model of switching from non-glycopeptide to glycopeptide antibiotic prophylaxis for surgery**

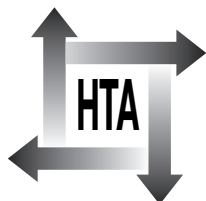
G Cranny, R Elliott, H Weatherly,  
D Chambers, N Hawkins, L Myers,  
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January 2008

**Health Technology Assessment**  
**NHS R&D HTA Programme**  
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The research reported in this issue of the journal was commissioned by the HTA Programme as project number 05/36/01. The contractual start date was in September 2005. The draft report began editorial review in May 2006 and was accepted for publication in April 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

### **A systematic review and economic model of switching from non-glycopeptide to glycopeptide antibiotic prophylaxis for surgery**

G Cranny,<sup>1</sup> R Elliott,<sup>2</sup> H Weatherly,<sup>3</sup> D Chambers,<sup>1</sup> N Hawkins,<sup>3</sup> L Myers,<sup>1</sup> M Sculpher<sup>3</sup> and A Eastwood<sup>1\*</sup>

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**Objectives:** To determine whether there is a level of methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence at which a switch from non-glycopeptide to glycopeptide antibiotics for routine prophylaxis is indicated in surgical environments with a high risk of MRSA infection.

**Data sources:** Major electronic databases were searched up to September 2005.

**Review methods:** The effectiveness review included controlled clinical trials comparing a glycopeptide with an alternative antibiotic regimen that reported effectiveness and/or adverse events. Controlled observational studies were also included for adverse events. The cost-effectiveness review included economic evaluations comparing glycopeptide prophylaxis with any alternative comparator. Study validity was assessed using standard checklists. The supplementary economic reviews assessed evaluations of non-glycopeptide antibiotic prophylaxis; evaluations where antibiotic resistance is a problem; methods of modelling resistance in infectious diseases; and developing a conceptual framework. An indicative decision analytic model was developed to compare vancomycin with a cephalosporin and with a combination of vancomycin and cephalosporin, using hip arthroplasty as an exemplar. Available data on, for example, surgical site infection (SSI) rates, MRSA rates, effectiveness of the antibiotics, were incorporated into the model. Costs were estimated from the perspective of the NHS.

**Results:** The effectiveness review included 16 randomised controlled trials, with a further three studies included for adverse events only. There was no evidence that glycopeptides were more effective than non-glycopeptides in preventing SSIs. Most of the trials

did not report either the baseline prevalence of MRSA at the participating surgical units or MRSA infections as an outcome. The cost-effectiveness review included five economic evaluations of glycopeptide prophylaxis. Only one study incorporated health-related quality of life and undertook a cost-utility analysis. None of the studies was undertaken in the UK and none explicitly modelled antibiotic resistance. The supplementary reviews provided few insights into how to assess cost-effectiveness in the context of resistance. No studies modelled cost-effectiveness alongside epidemiological models of resistance. There was little information regarding the impact of surgical infections on costs post-discharge and patient quality of life. The lack of available clinical evidence limited the development of the cost-effectiveness model and meant that the modelling could only be indicative in nature. The model can be used to show the threshold baseline risk at which the use of vancomycin as prophylaxis might be cost-effective (the model did not include teicoplanin). The indicative model suggests that the baseline risk of MRSA can be fairly modest at below the national average and it would still appear cost-effective to use glycopeptide prophylaxis. The model indicates that the use of glycopeptides as a form of prophylaxis in addition to a treatment for MRSA infections is unlikely to decrease the total usage and hence reduce the risk of future problems with glycopeptide-resistant bacteria.

**Conclusions:** There is insufficient evidence to determine whether there is a threshold prevalence of MRSA at which switching from non-glycopeptide to glycopeptide antibiotic prophylaxis might be clinically effective and cost-effective. Future research needs to address the complexities of decision-making relating to

the prevention of MRSA and infection control in general. Research including evidence synthesis and decision modelling comparing a full range of interventions for infection control, which extends to

other infections, not just MRSA, is needed. A long-term research programme to predict the pattern of drug resistance and its implications for future costs and health is also needed.



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## Glossary and list of abbreviations

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

### Glossary

**Adverse event** An abnormal or harmful effect caused by and attributable to exposure to an intervention, which is indicated by some result such as death, a physical symptom or visible illness. An effect may be classed as adverse if it causes functional or anatomical damage, causes irreversible change in the homeostasis of the organism or increases the susceptibility of the organism to other chemical or biological stress.

**Blinding (synonym: masking)** Keeping secret group assignment (e.g. to treatment or control) from the study participants or investigators. Blinding is used to protect against the possibility that knowledge of assignment may affect patient response to treatment, provider behaviours (performance bias) or outcome assessment (detection bias). Blinding is not always practical (e.g. when comparing surgery with drug treatment). The importance of blinding depends on how objective the outcome measure is; blinding is more important for less objective outcome measures such as pain or quality of life.

**Concealment of allocation** The process used to prevent foreknowledge of group assignment in a randomised controlled trial, which should be seen as distinct from blinding. The randomisation process should be administered by someone who is not responsible for recruiting participants, for example, a hospital pharmacy or a central office. Methods of assignment such as date of birth and case record numbers are open to manipulation. Adequate methods of allocation concealment include centralised randomisation schemes; randomisation schemes controlled by a pharmacy; numbered or coded containers in which capsules from identical-looking, numbered bottles are administered

sequentially; on-site computer systems, where allocations are in a locked unreadable file; and sequentially numbered opaque, sealed envelopes.

**Confidence interval (CI)** Quantifies the uncertainty in measurement. Usually reported as 95% CI, i.e. the range of values within which one can be 95% sure that the true values for the whole population lie.

**Cost-benefit analysis** An attempt to give the consequences of the alternative interventions a monetary value. In this way, the consequences can be more easily compared with the costs of the intervention. This involves measuring individuals' 'willingness to pay' for given outcomes, and can be difficult.

**Cost-consequence analysis** Costs are reported separately from health effects.

**Cost-effectiveness analysis** The consequences of the alternatives are measured in natural units, such as years of life gained. The consequences are not given a monetary value.

**Cost minimisation** When two alternatives are found to have equal efficacy or outcomes (consequences). Therefore, the only difference between the two is cost. This is sometimes considered to be a subtype of cost-effectiveness analysis.

**Cost-utility analysis** The consequences of alternatives are measured in 'health state preferences', which are given a weighting score. In this type of analysis, different consequences are valued in comparison with each other, and the outcomes (e.g. life-years gained) are

*continued*

## Glossary continued

adjusted by the weighting assigned. In this way, an attempt is made to value the quality of life associated with the outcome so that life-years gained become quality-adjusted life-years gained.

**Discounting** The process of converting future pounds sterling and future health effects to their present value.

**Dominance** The state when an intervention under study is both less costly and more effective than for the comparator(s).

**Economic evaluation** Comparative analysis of alternative course of action in terms of both their costs and effects.

**Effectiveness** The extent to which a specific intervention, when used under ordinary circumstances, does what it is intended to do.

**Extended dominance** The state when a strategy is both more costly and less effective than a linear combination of two other strategies with which it is mutually exclusive.

**Hemiarthroplasty** Arthroplasty where only the femur end of the hip joint is replaced with a prosthesis.

**Incidence** The number of new cases of a disease or event in a population during a specific period.

**Incremental cost-effectiveness ratio (ICER)** An expression of the additional cost of health gain associated with an intervention relative to an appropriate comparator. Expressed as the difference in mean costs (relative to the comparator) divided by the difference in mean effects. Sometimes expressed with confidence intervals.

**Intention-to-treat (ITT)** An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not. Intention-to-treat analyses are favoured in assessments of effectiveness as they mirror the non-compliance and treatment changes that are likely to occur when the intervention is used in practice and because of the risk of attrition bias when participants are excluded from the analysis.

**Methodological quality (synonyms: validity, internal validity)** The extent to which the design and conduct of a study are likely to have prevented systematic errors (bias). Variation in quality can explain variation in the results of studies included in a systematic review. More rigorously designed (better 'quality') trials are more likely to yield results that are closer to the 'truth'.

**p-Value** In the context of significance tests, the *p*-value represents the probability that a given difference is observed in a study sample, when such a difference does not exist in the relevant population. Small *p*-values indicate stronger evidence to reject the null hypothesis of no difference and a *p*-value of less than 0.05 indicates that a result is statistically significant.

**Prevalence** The measure of the proportion of people in a population who have some attribute or disease at a given point in time or during some time period.

**Primary resistance** This occurs when the initial infecting strain is resistant to standard treatment.

**Quality-adjusted life-year (QALY)** An index of health gain where survival duration is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

**Randomised controlled trial (RCT)** An experiment in which investigators randomly allocate eligible people into intervention groups to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the treatment and control groups.

**Relative risk (RR) (synonym: risk ratio)** The ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. An  $RR = 1$  indicates no difference between comparison groups. For undesirable outcomes, an  $RR < 1$  indicates that the intervention was effective in reducing the risk of that outcome.

*continued*

## Glossary continued

**Secondary resistance** This develops from an initially sensitive infecting strain in an individual during treatment.

**Sensitivity analysis** A mathematical method that examines uncertainty associated with parameter estimated into the analysis to test the robustness of the analysis findings. In one-way sensitivity analysis each parameter is varied individually, for multi-way analysis two or more parameters are varied at the same time, threshold analysis identifies the critical values above or below which the results of a study vary and analysis of extremes is used to examine the most pessimistic and the most optimistic scenarios. Finally, probabilistic sensitivity analysis attributes distributions of probabilities to uncertain variables that are incorporated within a model.

**Systematic review** A review of a clearly formulated question that uses systematic and

explicit methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review.

**Time trade-off (TTO)** Measuring a health state by trading off life-years in a state of less than perfect health for a shorter life span in a state of perfect health.

**Utility** A measure of the strength of an individual's preference for a given health state or outcome. Utilities assign numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health), and provide a single number that summarises health.

**Values** An alternative measure of the strength of an individual's preference for a given health state or outcome. In contrast to utilities, values reflect preferences elicited in a risk-less context.

## List of abbreviations

ACT	artemisinin-based combination therapy	DALY	disability-adjusted life-year
ADR	adverse drug reaction	DOT	directly observed therapy
AE	adverse event	ENT	ear, nose and throat
ASA	American Society of Anesthesiology	GART	genotypic resistance screening
CABG	coronary artery bypass graft	GDP	gross domestic product
CCT	controlled clinical trial	GISA	glycopeptide intermediate-resistance <i>Staphylococcus aureus</i>
CDC	Centers for Disease Control	GRSA	glycopeptide-resistant <i>Staphylococcus aureus</i>
CGE	computable general equilibrium	HAART	highly active anti-retroviral therapy
CI	confidence interval	HAI	hospital-acquired infection
CNS	coagulase-negative staphylococci	HIV	human immunodeficiency virus
CPS	coagulase-positive staphylococci	HRQoL	health-related quality of life
CRD	Centre for Reviews and Dissemination	ICER	incremental cost-effectiveness ratio
CRPF	chloroquine-resistant <i>Plasmodium falciparum</i>		

continued

**List of abbreviations continued**

ICU	intensive care unit	QALY	quality-adjusted life-year
IgE	immunoglobulin E	QoL	quality of life
ITT	intention-to-treat	RCT	randomised controlled trial
LOS	length of hospital stay	RR	relative risk
MDR	multi-drug resistant	SD	standard deviation
MR-CNS	methicillin-resistant coagulase-negative staphylococci	SF-36	Short Form with 36 Items
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>	SIGN	Scottish Intercollegiate Guidelines Network
MRSE	methicillin-resistant <i>Staphylococcus epidermidis</i>	SSI	surgical site infection
MSSA	methicillin-susceptible <i>Staphylococcus aureus</i>	SSISS	Surgical Site Infection Surveillance Service
NICE	National Institute for Health and Clinical Excellence	TB	tuberculosis
NNIS/ NNISS	National Nosocomial Infection Surveillance Service	VISA	vancomycin intermediate-resistance <i>Staphylococcus aureus</i>
OR	odds ratio	VR	valve replacement
PSS	Personal Social Services	VRE	vancomycin-resistant enterococci
		VRSA	vancomycin-resistant <i>Staphylococcus aureus</i>

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



## Executive summary

### Background

Surgical site infections (SSIs) are a major cause of morbidity and mortality in surgical patients. Antibiotic prophylaxis is recommended when the risk of infection is high and/or the consequences of infection are likely to be severe. In recent years, the prevalence of antibiotic-resistant bacteria has increased markedly, methicillin-resistant *Staphylococcus aureus* (MRSA) being a cause of particular concern. Glycopeptide antibiotics (vancomycin and teicoplanin) are active against MRSA, but are normally reserved for the treatment of MRSA infections because of the perceived risk of selecting new resistant strains by increasing glycopeptide use. This project considers the implications of switching from non-glycopeptide to glycopeptide antibiotics for surgical prophylaxis.

### Objectives

Our overall objective was to determine whether there is a level of MRSA prevalence at which a switch from non-glycopeptide to glycopeptide antibiotics for routine prophylaxis is indicated in surgical environments with a high risk of MRSA infection. We addressed this question by undertaking:

- a systematic review of the effectiveness of glycopeptide compared with non-glycopeptide antibiotic prophylaxis to determine whether there is evidence to guide antibiotic choice for surgical prophylaxis at different levels of MRSA prevalence
- a systematic review of published economic evaluations, to examine the cost-effectiveness of glycopeptide antibiotics compared with appropriate comparators
- a series of supplementary reviews, to support the modelling work and associated research recommendations
- a modelling approach to estimate the cost-effectiveness of glycopeptide antibiotic prophylaxis relative to appropriate comparators, using orthopaedic surgery as an exemplar.

### Methods

#### Systematic reviews

We searched 11 databases from 1990 to September 2005. Internet searches and searching of the reference lists of included papers were also performed. NHS EED, HEED and IDEAS were also searched for the cost-effectiveness review and modelling.

The effectiveness review included controlled clinical trials, comparing a glycopeptide with an alternative antibiotic regimen in adults undergoing surgical procedures where prophylaxis is recommended, that reported effectiveness and/or adverse events. Controlled observational studies were also included for adverse events. The cost-effectiveness review included economic evaluations comparing glycopeptide prophylaxis with any alternative comparator. Study validity was assessed using standard checklists.

#### Supplementary reviews

The supplementary economic reviews assessed evaluations of non-glycopeptide antibiotic prophylaxis; evaluations where antibiotic resistance is a problem; methods of modelling resistance in infectious diseases; and developing a conceptual framework.

#### Economic modelling

An indicative decision analytic model was developed to compare vancomycin with a cephalosporin and with a combination of vancomycin and cephalosporin, using hip arthroplasty as an exemplar. Available data on SSI rates, MRSA rates, effectiveness of the antibiotics in reducing infections and consequences of infection [impact on survival, length of hospital stay, health-related quality of life (HRQoL) and treatment intensity] were incorporated into the model. Costs were estimated from the perspective of the NHS.

### Results

#### Systematic reviews

The effectiveness review included 16 randomised controlled trials, with a further three studies

included for adverse events only. There was no evidence that glycopeptides were more effective than non-glycopeptides in preventing SSIs. Most of the trials did not report either the baseline prevalence of MRSA at the participating surgical units or MRSA infections as an outcome. The cost-effectiveness review included five economic evaluations of glycopeptide prophylaxis. Only one study incorporated HRQoL and undertook a cost-utility analysis. None of the studies was undertaken in the UK, limiting the generalisability of the results to the UK, and none explicitly modelled antibiotic resistance.

### **Supplementary reviews**

The supplementary reviews provided few insights into how to assess cost-effectiveness in the context of resistance. No studies modelled cost-effectiveness alongside epidemiological models of resistance. In addition, there was little information regarding the impact of surgical infections on costs post-discharge and patient quality of life.

### **Economic modelling**

The lack of available clinical evidence limited the development of the cost-effectiveness model and meant that the modelling could only be indicative in nature. Hip arthroplasty was chosen as an exemplar because it is a 'clean' procedure and patients are at high risk of MRSA. The model can be used to show the threshold baseline risk at which the use of vancomycin as prophylaxis might be cost-effective (the model did not include teicoplanin). The indicative model suggests that the baseline risk of MRSA (the average risk of MRSA infection in the population of patients undergoing hip arthroplasty in a given centre) can

be fairly modest at below the national average and it would still appear cost-effective to use glycopeptide prophylaxis. However, this conclusion is reached in the absence of any modelling of the effect on resistance caused by increased glycopeptide use. The model indicates that, at all plausible baseline infection rates, the use of glycopeptides as a form of prophylaxis in addition to a treatment for MRSA infections is unlikely to decrease the total usage and hence reduce the risk of future problems with glycopeptide-resistant bacteria.

## **Conclusions**

### **Implications for healthcare**

There is insufficient evidence to determine whether there is a threshold prevalence of MRSA at which switching from non-glycopeptide to glycopeptide antibiotic prophylaxis might be clinically effective and cost-effective.

### **Recommendations for research**

Future research needs to address the complexities of decision-making relating to the prevention of MRSA and infection control in general. Focusing on MRSA alone is too limited and the prophylactic use of glycopeptides is only one aspect of infection control.

Research including evidence synthesis and decision modelling comparing a full range of interventions for infection control, which extends to other infections, not just MRSA, is needed. A long-term research programme to predict the pattern of drug resistance and its implications for future costs and health is also needed.

# Chapter 1

## Background

Hospital acquired infections (HAIs) are a major source of morbidity and mortality in the NHS and surgical site infection (SSI) is one of the most common types of HAI.<sup>1</sup> Recent surveillance data from 102 English hospitals suggest that developing an SSI extends the patient's hospital stay by an average of 9 days, and up to 21 days for limb amputation, resulting in an additional cost ranging from £959 to £6103.<sup>2</sup> When these SSIs are deep incisional or organ space infections, they also result in a substantial increase in risk of 30-day mortality, with odds ratios of 6.8 for vascular surgery and 2.5 for hip prosthesis surgery.<sup>2</sup>

Prophylactic administration of antibiotics in the pre- or perioperative period may reduce the risk of SSIs and other infections by inhibiting bacterial growth and adherence to prosthetic implants. Prophylaxis is not always indicated but is appropriate when the risk of infection is high and/or the consequences of any infection are likely to be severe (for example, in total hip replacement). Guidelines produced by the Scottish Intercollegiate Guidelines Network (SIGN)<sup>3</sup> (being updated at the time of writing this report) recommend prophylaxis for a wide range of surgical procedures classified as clean (no inflammation and no opening of the respiratory, alimentary or genitourinary tracts), clean-contaminated (respiratory, alimentary or genitourinary tracts are entered without significant spillage) or contaminated [acute inflammation or visible wound contamination (without pus) is present].

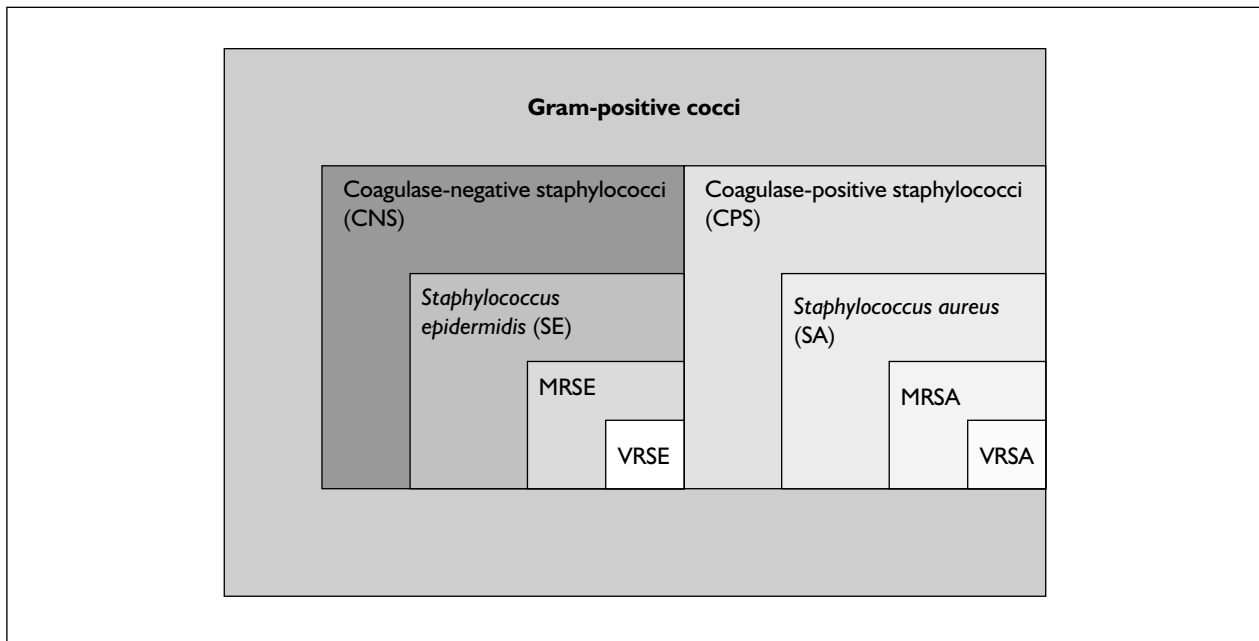
A range of different types of antibiotics with different modes of action is available for use in surgical prophylaxis. The cephalosporins have been most widely used and studied but regimens involving cephalosporins for surgical prophylaxis probably need to be reassessed for efficacy since vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) have become more prevalent in the UK.<sup>4</sup> Other major antibiotic families include penicillins and other  $\beta$ -lactams, glycopeptides (vancomycin, teicoplanin), aminoglycosides (gentamicin, tobramycin, netilmicin and amikacin), macrolides (erythromycin and clarithromycin), quinolones/fluoroquinolones (ciprofloxacin,

levofloxacin, norfloxacin and others), metronidazole, tetracyclines, sulfonamides, clindamycin, chloramphenicol and fusidic acid. Penicillins, glycopeptides, aminoglycosides and metronidazole are the principal agent groups used in surgical prophylaxis.

Most of the bacterial species causing SSIs can be categorised as either Gram-positive or Gram-negative, depending on how they respond to a Gram stain procedure. Bacteria are also either spherical (cocci) or rod-shaped (bacilli). These two criteria are easily visible by microscope and give rise to four easily identifiable subgroups of bacteria: Gram-positive cocci, Gram-positive bacilli, Gram-negative cocci and Gram-negative bacilli. Staphylococci may or may not have the enzyme coagulase, and their response to a test further divides them into 'coagulase-positive' or 'coagulase-negative' species.

*Staphylococcus aureus* (found on the skin and nares of about 30% of the population) is a coagulase-positive species and *Staphylococcus epidermidis* (found on the skin) is a coagulase-negative species (Figure 1). All species of staphylococci, both coagulase-positive and coagulase-negative, have developed resistance to many antibiotics. These are known as 'methicillin (or multi-) resistant'. This gives rise to MRSA and methicillin-resistant *Staphylococcus epidermidis* (MRSE). Primary resistance occurs when the initial infecting strain is resistant to standard treatment. Secondary resistance develops from an initially sensitive infecting strain in an individual during treatment.

The prevalence of MRSA has increased markedly over the last 10 years. Data on SSIs in hospitals in England indicate that during 1997–2002, 49% of causal organisms identified were staphylococci, of which 81% were *S. aureus*.<sup>5</sup> The majority of *S. aureus* strains (63%) were MRSA. Although not a particularly virulent pathogen, MRSA can be difficult to treat and because of its concentration in hospitals, nursing homes and other care facilities it disproportionately affects the elderly and other vulnerable groups. The prevalence of MRSA infection in the community is also increasing, although cases mainly occur among



**FIGURE 1** Gram-positive cocci families. VRSA, Vancomycin-resistant *Staphylococcus aureus*; VRSE, Vancomycin-resistant *Staphylococcus epidermidis*

people who have recently been in contact with the healthcare system.<sup>4</sup>

Glycopeptide antibiotics are active against Gram-positive bacteria, including MRSA. Vancomycin was introduced during the 1950s and has generally been reserved for treatment of infections for which other antibiotics cannot be used because of patient sensitivity or bacterial resistance. Teicoplanin has similar activity to vancomycin but has a longer duration of action. Other glycopeptide antibiotics are still under investigation (oritavancin, ramoplanin) or are only used in animals (avoparcin). The SIGN guidelines do not recommend the use of glycopeptide antibiotics for prophylaxis because of lack of evidence of clinical benefit and concern that overuse of these drugs may increase the prevalence of vancomycin-resistant bacteria.<sup>3</sup> Similarly guidelines produced by the US Centers for Disease Control (CDC) in 1999 do not recommend vancomycin for routine prophylaxis, although they state that vancomycin may be the agent of choice in the presence of a cluster of MRSA infections or incisional SSIs caused by other methicillin-resistant bacteria.<sup>6</sup>

MRSA strains vary in their antibiotic resistance profiles. Methicillin-susceptible *S. aureus* (MSSA) may also possess acquired resistance to multiple antibiotics and be a source of new resistance combinations for MRSA. A survey of UK hospitals in 2004 found that 88% of MRSA isolates were resistant to three or more classes of antibiotics,

93% were resistant to fluoroquinolones and 81% to macrolides and over 99% of strains were reported as fully susceptible to glycopeptide antibiotics (vancomycin and teicoplanin).<sup>4</sup> However, vancomycin resistance has been detected in enterococci and subsequently in *S. aureus*<sup>7,8</sup> and MRSA strains with reduced susceptibility to teicoplanin have been identified in the UK<sup>9</sup> and France.<sup>10</sup> Depending on the mechanism of resistance, these strains are variably referred to as vancomycin-resistant *S. aureus* (VRSA), glycopeptide-resistant *S. aureus* (GRSA), vancomycin intermediate-resistance *S. aureus* (VISA) and glycopeptide intermediate-resistance *S. aureus* (GISA).

From the viewpoint of the NHS and other national healthcare systems, SSIs caused by MRSA and other methicillin-resistant bacteria are primarily an issue in cardiac, vascular and orthopaedic surgery. Current recommendations for prophylaxis of infection in patients undergoing surgery are that glycopeptides should be limited to those with known MRSA infection or colonisation in order to limit selection for new glycopeptide-resistant strains.<sup>4</sup> However, if prophylactic treatment with a single dose of a glycopeptide can prevent the development of an infection requiring longer treatment, possibly with higher doses, routine prophylaxis might have the effect of reducing overall antibiotic use. Some sources recommend the use of brief courses of vancomycin for prophylaxis in institutions where the prevalence of



MRSA and MRSE is high, arguing that the benefits in terms of reducing the environmental pressure that promotes the development of vancomycin resistance and reducing the risk of superinfections caused by other bacteria and yeasts outweigh the risks.<sup>11</sup> Although resistance to glycopeptides may be rare in the UK at present, the risk of new resistant strains emerging should be taken into account in determining policies for antibiotic use.

This study attempts to determine whether there is a threshold of MRSA prevalence at which switching to routine prophylaxis with a glycopeptide-based antibiotic regimen might be clinically effective and cost-effective. The individual patient's risk of developing an MRSA infection is affected by a

range of policies, for example screening, patient isolation and prevention of transmission by healthcare staff. Screening for MRSA colonisation/infection and if necessary eradicating the organism before surgery have particular relevance to the risk of SSI caused by MRSA. The broader aspects of infection control that inform the perioperative and postoperative prevention and treatment of SSI will be dealt with in guidelines from the National Institute for Health and Clinical Excellence (NICE) that were under development at the time of writing this report (<http://www.nice.org.uk/page.aspx?o=299840>). Antibiotic prophylaxis was excluded from the scope of these guidelines but an update of the SIGN guidelines<sup>3</sup> is due to be published in 2007.



## Chapter 2

# Aims and objectives

The overall objective of the project was to determine whether there is a level of MRSA prevalence at which a switch from non-glycopeptide to glycopeptide antibiotics for routine prophylaxis is indicated in surgical environments with a high risk of MRSA infection. We attempted to answer this question using a number of different approaches:

1. A systematic review of the effects of glycopeptide antibiotics compared with non-glycopeptide antibiotics on MRSA infection, overall infections, other morbidity and mortality, adverse events and occurrence and transmission of glycopeptide resistance in patients undergoing surgical procedures with a high risk of SSI or other postoperative infections. The objective of this review was to determine whether there is evidence from controlled clinical trials to guide antibiotic choice for surgical prophylaxis at different levels of MRSA prevalence.
2. A systematic review of published economic evaluations, to examine the cost-effectiveness of glycopeptide antibiotics compared with appropriate comparators.
3. A series of supplementary reviews, to support the modelling work and associated research recommendations. These involved reviews of:
  - economic evaluations of non-glycopeptide prophylaxis for surgery; economic evaluations assessing cost-effectiveness in areas of infectious disease where drug resistance is an issue; use of epidemiological and decision analytic techniques to model antibiotic resistance; and conceptual papers which might contribute to a framework for the economic evaluation of policies against MRSA.
4. A modelling approach to estimate the cost-effectiveness of glycopeptide antibiotic prophylaxis relative to appropriate comparators. In view of the range of different types of surgery and the time and resources available, we decided to focus on orthopaedic surgery (hip arthroplasty) as an exemplar of surgery where antibiotic prophylaxis is strongly recommended, and where there is evidence of its effectiveness from clinical trials.<sup>3</sup> Our objective was to develop a model that incorporated the effects of different treatment strategies on the risk of infection and that included patient, environmental and procedural variables related to the risk of MRSA infection. An additional objective was to seek to incorporate into the model evidence on the occurrence and transmission of glycopeptide-resistant organisms.



## Chapter 3

# Systematic review of effectiveness

### Methods

This systematic review aimed to establish the effectiveness of glycopeptide antibiotic prophylaxis compared with any other antibiotic prophylaxis, and to summarise adverse events related to the use of glycopeptide prophylaxis. It was undertaken following the guidelines for undertaking systematic review produced by the Centre for Reviews and Dissemination (CRD).<sup>12</sup>

### Search strategy

We searched the following databases from 1990 to September 2005: MEDLINE, EMBASE, CINAHL, CENTRAL, Science Citation Index and BIOSIS. The cut-off date of 1990 was chosen after discussion with clinical experts as MRSA was unlikely to have been reported in trials published before 1990.

The search strategies used for all databases are presented in Appendix 1. In addition, information on studies in progress, unpublished research or research reported in the grey literature was sought by searching the following databases: ISI Proceedings; Science and Technology Edition; Inside Conferences; National Research Register; metaRegister of Controlled Trials; and the National Technical Information Service. No language restrictions were applied.

Internet searches were also carried out using the specialist search engine OMNI (<http://www.omni.ac.uk>) and the meta-search engine Copernic (<http://www.copernic.com>).

Attempts to identify further studies were made by examining the reference lists of all retrieved articles.

### Study selection

Study selection was a two-stage process. Initially, the titles and abstracts of items retrieved by the literature search were screened for relevance by two reviewers independently. Full copies of all potentially relevant papers were obtained. These were then assessed for inclusion by two reviewers. Disagreements were resolved by discussion, with referral to a third reviewer if necessary.

### Inclusion criteria

In order to be included in the review a study had to meet all of the following criteria.

#### Study design

- **Effectiveness:** controlled clinical trials (CCTs) (randomised or quasi-randomised) investigating the use of glycopeptide antibiotics for prophylaxis compared with any alternative prophylactic antibiotic regimen.
- **Adverse events:** CCTs (randomised or quasi-randomised) comparing a prophylactic glycopeptide regimen with any alternative prophylactic antibiotic regimen. Controlled observational studies of a glycopeptide antibiotic regimen, compared with any alternative antibiotic regimen, when used for surgical prophylaxis.

#### Participants

Participants were all adult patients (as defined by the studies) undergoing surgical procedures.

#### Types of surgery

The following surgical procedures had been used (both traditional and minimally invasive surgery), where antibiotic prophylaxis is recommended by the SIGN guidelines:<sup>3</sup>

- **Clean-contaminated surgery:** procedures with a high risk of bacterial contamination where the respiratory, gastrointestinal, urinary or genital tracts are opened.
- **Clean surgery:** procedures with a low risk of contamination where none of the above viscera are opened, but which require prophylaxis because serious complications could result from an infection. Cardiac, vascular and any procedures involving an implant (orthopaedic or vascular) are included in this category.

Studies of contaminated procedures (involving major breaks in sterile technique, significant spillage from the gastrointestinal tract, fresh open wounds or acute inflammation), dirty procedures (involving pre-existing infection or perforated viscera), infections as indication for surgery (appendicitis, cholecystitis, diverticulitis, salpingitis) and where further surgery was required

after or because of a surgical site infection were excluded from the review.

### Interventions

The intervention of interest was pre- or intraoperative administration of glycopeptide antibiotics (vancomycin, teicoplanin, ramoplanin and decaplanin) compared with any alternative antibiotic regimen. Postoperative administration was excluded. All routes of administration were considered. Multiple doses of antibiotic, continuing after surgery is complete, were considered provided that the initial dose was administered either before or during surgery. Both monotherapy and multiple drug regimens were eligible.

### Outcome measures

#### Effectiveness

- **Primary outcomes:** the occurrence of an SSI, MRSA infection, any other infection (e.g. sepsis or bacteraemia) and mortality. SSIs were categorised as superficial, deep or organ space, where reported. The primary period was any infection that occurred within 30 days of surgery, although late infections occurring after 1 month from surgery were also reported.
- **Secondary outcomes:** length of postoperative hospital stay, rehospitalisation, reoperation, morbidity or disability and adverse events (AEs).

#### Adverse events

Any reported AEs considered to be related to the antibiotic prophylaxis.

### Data extraction

Data were extracted by one reviewer and checked for accuracy and consistency by a second reviewer. Disagreements were resolved by discussion, with referral to a third reviewer if necessary.

The following information was extracted: study details and aims, study population, surgery details, details of the interventions (glycopeptide and comparator(s)), results (primary and secondary outcomes, organism causing infection, AEs) and study conclusions.

For studies included for AEs only, study, participant and surgery details were extracted as for the CCTs. Details of the glycopeptide regimen and full details of any AEs, their severity, relationship to the antibiotic and numbers of patients affected were extracted.

### Quality assessment

Included CCTs were assessed for methodological quality based on the following study characteristics:

randomisation, allocation concealment, similarity of treatment groups at baseline, specification of eligibility criteria, blinding (of outcome assessors and patients), intention-to-treat (ITT) analysis, sample size calculation and reporting of withdrawals (see Appendix 2 for quality checklists). The planned quality assessment of controlled observational studies was not performed as the only observational study included was published as an abstract. Quality assessments were carried out independently by two reviewers. Any disagreements were resolved by discussion, with referral to a third reviewer if necessary.

### Data analysis

For each dichotomous outcome, the numbers of patients experiencing the outcome were extracted for each treatment group. The relative risk (RR) and 95% confidence interval (CI) were calculated for each trial on an ITT basis where possible. Continuous data were analysed by calculating the difference in means and corresponding 95% CI for each trial.

No statistical pooling was performed because of clinical heterogeneity between the studies due to differences in surgical procedures, comparator antibiotics, dose and timing of both glycopeptide and comparator regimens. The study results are presented in Forest plots and described in a narrative synthesis, grouped by outcome and surgical specialty.

Statistical analyses were performed using StatsDirect statistical software ([www.statsdirect.com](http://www.statsdirect.com)). This calculates 95% CIs for the RR using the method of Koopman.

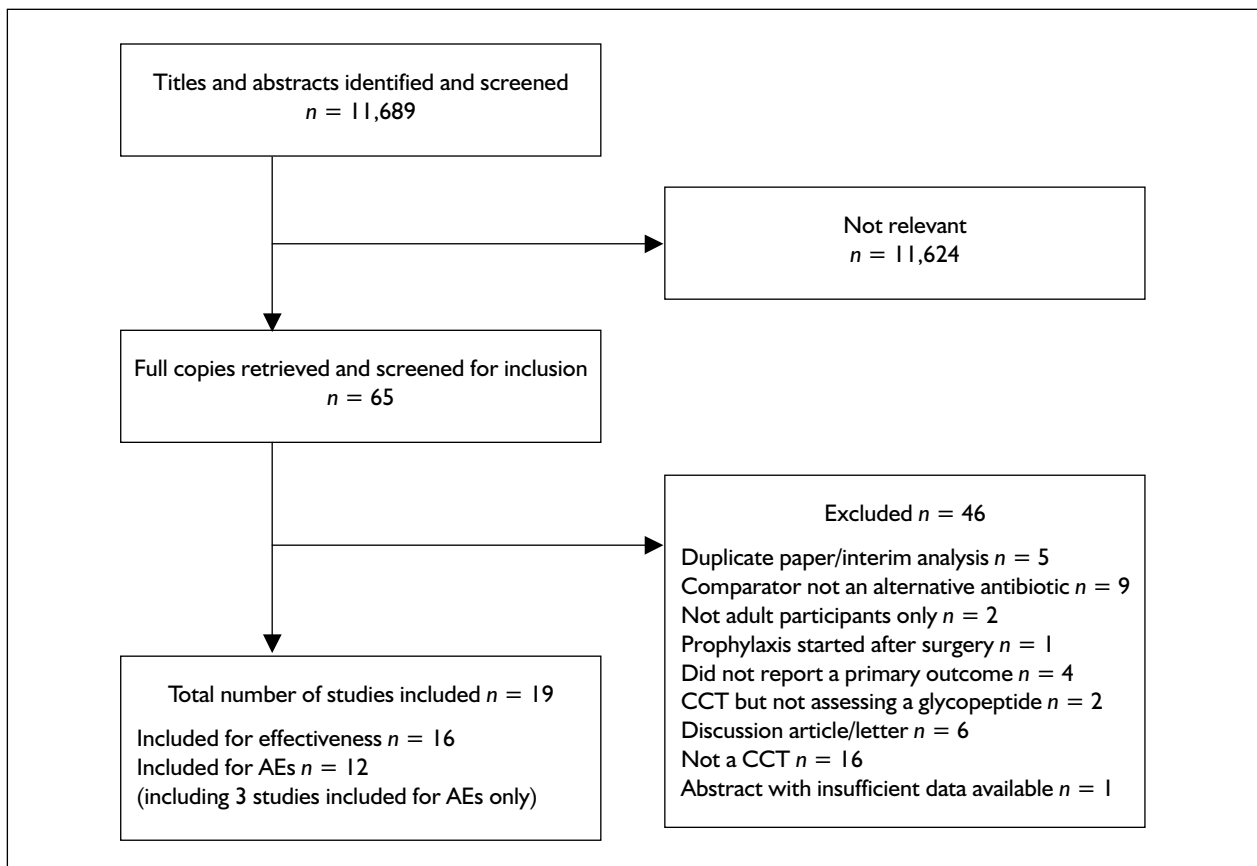
## Results

### Identified studies

The literature searches identified 11,689 references. These were screened for relevance and 65 were considered to be potentially relevant. These 65 articles were assessed using the predefined inclusion criteria. *Figure 2* shows the flow of studies through the review process and the number of studies excluded. Full details of the excluded studies, together with the reasons for exclusion, are presented in Appendix 3.

### Nature of the evidence

A total of 19 studies met the review inclusion criteria, with 16 studies providing results on clinical effectiveness and 12 studies providing



**FIGURE 2** Flow chart of studies through the review process

results on AEs (three of these studies were included for AEs only). All studies, apart from one Spanish trial,<sup>13</sup> were reported in English. Three studies<sup>14–16</sup> were published as an abstract only.

The 16 studies included for effectiveness were all randomised controlled trials (RCTs). Five trials were in cardiac surgery;<sup>13,17–20</sup> one trial included both cardiac and vascular procedures;<sup>21</sup> three trials were in vascular surgery;<sup>16,22,23</sup> five trials were in orthopaedic surgery;<sup>14,24–27</sup> one trial was in neurosurgery;<sup>28</sup> and one trial was in thoracic surgery.<sup>29</sup> Most trials compared vancomycin or teicoplanin with a cephalosporin. The trial of cardiac and vascular surgery by Maki and colleagues<sup>21</sup> included two cephalosporin arms, cefazolin and cefamandole. As the trial reported comparisons of vancomycin versus the combined cephalosporin arms for the primary outcome of SSI, the results of the two cephalosporin arms have been combined in this review. Three trials compared a glycopeptide to an alternative glycopeptide regimen: one cardiac trial compared vancomycin with teicoplanin;<sup>13</sup> one orthopaedic trial compared 400 mg of teicoplanin given regionally with 800 mg given systemically;<sup>27</sup> and a

trial of thoracic surgery in lung cancer patients compared long-term teicoplanin administration with short-term teicoplanin administration.<sup>29</sup>

An overview of the studies included for effectiveness detailing the surgical procedures, length of follow-up, prophylaxis regimens and outcomes reported is presented in *Table 1* and an overview of the studies included for AE results only is presented in *Table 2*. Full details of all studies are presented in the data extraction tables in Appendix 4.

### Quality assessment

The results of the quality assessment are summarised in *Table 3*, for studies included for effectiveness and those included for AEs only. Three studies<sup>14–16</sup> were published in abstract form without enough information to allow a meaningful assessment of study quality and have been omitted from the table.

Of the 16 trials included for effectiveness, six used methods considered to produce true randomisation, including the use of computer programs,<sup>13,28</sup> random number tables,<sup>20,25</sup> permuted blocks<sup>22</sup> and

TABLE 1 Details of studies included for effectiveness

Study	Surgery details	N	Follow-up	Glycopeptide	Comparator(s)	Outcomes reported
<i>Cardiac surgery</i> Codina, 2000, Spain <sup>13</sup>	CABG or VR	500	Not reported	<b>Vancomycin:</b> 1 g at induction (plus netilmicin 150 mg) 2nd dose for VR	<b>Teicoplanin:</b> 400 mg at induction (plus netilmicin 150 mg), 2nd dose for VR	SSI (CDC definition), AE, costs
Finkelstein, 2002, Israel <sup>17</sup>	CABG (chest, chest + leg), implant, other	1032	Hospital stay (daily), up to 1 year	<b>Vancomycin:</b> 1 g at induction, 1 g at 12 h	<b>Cefazolin:</b> 1 g at induction, 1 g at 8 and 16 h	SSI (CDC definition), other infections; bacteria (SSI, other), mortality, LOPS
Sagunur, 2000, Canada <sup>18</sup>	CABG, VR or both	3047	Discharge, 1 and 6 months	<b>Teicoplanin:</b> 15 mg/kg within 30 minutes of incision, then every 8 h for 6 doses	<b>Cefazolin:</b> 2 g within 30 minutes of incision, 1 g every 8 h for 6 doses	SSI, other infections, bacteria (SSI), mortality, morbidity, LOPS, re-hospitalisation, AE
Salminen, 1999, Finland <sup>19</sup>	CABG, graft or valve repair, aortic reconstruction	200	Hospital stay, 2 months	<b>Vancomycin:</b> 500 mg 45–60 minutes before incision, every 6 h for 48 h	<b>Ceftriaxone:</b> 2 g 45–60 minutes before incision	SSI, other infections, bacteria (SSI)
Vuorisalo, 1998, Finland <sup>20</sup>	CABG without valve surgery	1061	Hospital stay, 1 month	<b>Vancomycin:</b> 1 g at induction, 1 g at 12 h	<b>Cefuroxime:</b> 1.5 g over 15 minutes at induction, 0.75 g at 8 and 16 h	SSI (CDC definition), bacteria (SSI), mortality, LOPS
<i>Cardiac/vascular surgery</i> Maki, 1992, USA <sup>21</sup>	<i>Cardiac:</i> CABG, prosthetic VR <i>Vascular:</i> aortic aneurysm repair, bypass graft	334	Hospital stay (daily), 3 months	<b>Vancomycin:</b> 15 mg/kg or 1 g starting 30 minutes before incision, 500 mg every 6 h for 48 h	<b>Cefamandole:</b> 2 g starting 30 minutes before incision, every 6 h for 48 h <b>Cefazolin:</b> 1 g starting 30 minutes before incision, every 6 h for 48 h	SSI, other infections, bacteria (SSI, other), LOPS, AE
<i>Vascular surgery</i> Kester, 1999, UK <sup>23</sup>	Grafts, aneurysm repair, bypass, carotid surgery profundaplasty	272	28 days post-surgery, 6 months	<b>Teicoplanin:</b> 6 mg/kg at induction (2nd intraoperative dose for surgery > 3 h)	<b>Cefradine:</b> 1 g at induction, 8, 16 h (2nd intraoperative dose for surgery > 3 h), plus metronidazole 1 g rectally <b>Cefamandole:</b> 3 doses (exact: dosage not given)	SSI (suspected and proven), other infections, bacteria (SSI), mortality, LOPS, AE
Kirtzis, 1991, France (abstract only) <sup>16</sup>	Procedures involving the groin	202	Not reported	<b>Vancomycin:</b> 2 g/day over 3 days	<b>Cefazolin:</b> 2 g at induction	SSI, bacteria (SSI)
Marroni, 1999, Italy <sup>22</sup>	Abdominal and lower extremity peripheral vascular procedures	238	Hospital stay (daily), 1 year (every 3 months)	<b>Teicoplanin:</b> 400 mg at induction		SSI (CDC definition), other infections, bacteria (SSI), mortality

continued



TABLE 1 Details of studies included for effectiveness (cont'd)

Study	Surgery details	N	Follow-up	Glycopeptide	Comparator(s)	Outcomes reported
<i>Orthopaedic surgery</i> Caprioli, 1995, Italy (abstract only) <sup>14</sup>	Hip or elbow prosthetic surgery	174	Not reported	<b>Vancomycin:</b> 1 g given 2 h before surgery (plus gentamicin 80 mg)	<b>Cefamandole:</b> 2 g given 1 h before surgery, 1 g at end of surgery	Wound infections, other infections
de Lalla, 1993, Italy <sup>27</sup>	Monolateral or bilateral total knee replacement	24	Post- operative, 12–26 months	<b>Teicoplanin (regional):</b> 400 mg in foot vein of leg(s) straight after tourniquet inflation	<b>Teicoplanin (systemic):</b> 800 mg in forearm vein 2.5 h before surgery	SSI (post-operative and at 12 months)
Mollan, 1992 (interim analysis), UK <sup>26</sup>	Total hip or knee replacement	850	30 days and 6–18 months	<b>Teicoplanin:</b> 400 mg at induction (plus gentamicin bone cement)	<b>Cefamandole:</b> 2 g at induction, 1 g at 6, 12, 18 h (plus gentamicin bone cement)	SSI, bacteria (SSI), other infections, mortality, AE
Periti, 1999, Italy <sup>24</sup>	Primary hip or knee replacement	860	Hospital stay (daily), 3 and 12 months	<b>Teicoplanin:</b> 400 mg at induction	<b>Cefazolin:</b> 2 g at induction, 1 g every 6 h for 24 h	SSI (post-operative, 3 and 12 months), bacteria (SSI), other infections, LOPS, AE
Suter, 1994, Italy <sup>25</sup>	Elective total hip replacement (conventional theatre)	520	At least 12 months	<b>Teicoplanin:</b> 400 mg 60–90 minutes before surgery	<b>Cefamandole:</b> 2 g 60–90 minutes before and 1 g at end of surgery	SSI (infected superficial haematoma), other infections, mortality, LOPS, AE
<i>Other surgical procedures</i> Pons, 1993, USA <sup>28</sup>	Neurosurgery: cranial, spinal, transsphenoidal	910	Hospital stay (daily), 3 months (monthly)	<b>Vancomycin:</b> 1 g 1 h before incision (plus 80 mg gentamicin)	<b>Ceftizoxime:</b> 2 g, 1 h before incision	SSI, bacteria (SSI), other infections, AE
Ratto, 1990, Italy <sup>29</sup>	Thoracic: lobectomy, pneumonecctomy, wedge resections	102	Hospital stay (twice daily)	<b>Teicoplanin (long-term):</b> as short-term continued every 12 h until drain removal	<b>Teicoplanin (short-term):</b> 6 mg/kg at induction, 2 doses of 3 mg/kg every 8 h (plus 1 g aztreonam)	SSI (wound, pleural space), bacteria (SSI), other infections, AE

AE, adverse event; CABG, coronary artery bypass graft; LOPS, length of post-operative hospital stay; SSI, surgical site infection; VR, valve replacement.

TABLE 2 Details of studies included for adverse events only

Study	Study design	Surgery details	N	Follow-up	Glycopeptide	Comparator(s)	Outcomes reported
Mercieri, 1999, Italy <sup>30</sup>	RCT assessing the effect of prophylaxis on kidney function	Cardiac: elective coronary artery surgery	100	Not reported	<p><b>Vancomycin:</b> 15 mg/kg given 3 h before surgery, 10 mg/kg after CPB interruption, then 15 mg/kg every 12 h for 48 h (plus gentamicin 1.5 mg/kg after first vancomycin dose then every 8 h for 48 h)</p> <p><b>Vancomycin plus aprotinin:</b> as for vancomycin group plus high-dose aprotinin (<math>2 \times 10^6</math> kiu over 15 minutes at induction, then continuous infusion of <math>5 \times 10^5</math> kiu/h with an additional dose of <math>2 \times 10^6</math> kiu added to CPB solution)</p>	<p><b>Cefamandole:</b> 2 g 30 minutes before surgery, then every 6 h for 48 h</p> <p><b>Cefamandole plus aprotinin:</b> as for the cefamandole group with additional aprotinin as for the vancomycin plus aprotinin group</p>	AE (renal failure, changes in serum creatinine and cystatin C levels)
Miro, 1996, Spain (abstract only) <sup>15</sup>	Prospective study with historical control group	Cardiac: CABG, VR	1394	Not reported	<p><b>Vancomycin:</b> 1 g before surgery (plus 150 mg netilmicin). VR patients got 4 extra doses of 0.5 g every 6 h (plus 2 extra doses of 150 mg netilmicin every 12 h)</p>	<p><b>Teicoplanin:</b> 400 mg before surgery (plus 150 mg netilmicin). VR patients got an extra dose of 200 mg after surgery (plus 2 extra doses of 150 mg netilmicin every 12 h)</p>	AE (severe hypotension, red man's syndrome)
Romanelli, 1993, Canada <sup>31</sup>	RCT	Cardiac: CABG	58	Not reported	<p><b>Vancomycin:</b> 1 g slow infusion before induction, 500 mg in CPB solution, then 1 g every 2 h until chest tube discontinuation (plus cefazolin 1 g before induction, 1 g in CPB solution, then 1 g every 6 h for minimum 48 h)</p>	<p><b>Cefazolin:</b> 1 g before induction, 1 g in CPB solution, then 1 g every 6 h for minimum 48 h (plus placebo to match the vancomycin dosing schedule)</p>	AE (hypotension)

CPB, cardiopulmonary bypass; other abbreviations as in Table 1.

TABLE 3 Summary of quality assessment results

	Randomised	Randomisation method	Allocation concealment	Baseline comparability	Eligibility criteria specified	Blinding: outcome assessors	Blinding: patients	ITT analysis	Sample size calculation	Withdrawals reported
<b>Studies included for effectiveness</b>										
<i>Cardiac surgery</i>										
Codina, 2000 <sup>13</sup>	Yes	Computer program	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Finkelstein, 2002 <sup>17</sup>	No	Alternation	No	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes
Sagunur, 2000 <sup>18</sup>	Yes	Independent statistician	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Salminen, 1999 <sup>19</sup>	No	Alternation	No	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes
Vuorisalo, 1998 <sup>20</sup>	Yes	Random number table	Unclear	Yes	Yes	Unclear	Unclear	No	Unclear	Yes
<i>Cardiac/vascular surgery</i>										
Maki, 1992 <sup>21</sup>	Unclear	Not reported	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes
<i>Vascular surgery</i>										
Kester, 1999 <sup>23</sup>	Unclear	Sealed envelopes	No	Yes	Yes	No	No	Yes	Yes	Yes
Marroni, 1999 <sup>22</sup>	Yes	Permuted blocks	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
<i>Orthopaedic surgery</i>										
de Lalla, 1993 <sup>27</sup>	Unclear	Not reported	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Mollan, 1992 <sup>26</sup>	Unclear	Not reported	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	No
Periti, 1999 <sup>24</sup>	Unclear	Not reported	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes
Suter, 1994 <sup>25</sup>	Yes	Random number table	Unclear	Yes	Yes	Unclear	Unclear	No	Unclear	Unclear
<i>Other procedures</i>										
Pons, 1993 <sup>28</sup>	Yes	Computer program	Unclear	Unclear	Yes	Yes	Unclear	No	Unclear	Yes
Ratto, 1990 <sup>29</sup>	Unclear	Not reported	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes
<b>Adverse events only</b>										
<i>Cardiac surgery</i>										
Mercieri, 1999 <sup>30</sup>	Yes	Random number table	Unclear	Yes	Yes	Unclear	Unclear	No	Unclear	Unclear
Romanelli, 1993 <sup>31</sup>	Unclear	Not reported	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes

stratified randomisation by an independent statistician.<sup>18</sup> Two trials used randomisation by alternation of birth date or social security number,<sup>17,19</sup> which does not produce a genuinely random distribution between groups or conceal allocation of treatment. In the remaining trials, including four of the five in orthopaedic surgery, the method of randomisation was not reported. Concealment of treatment allocation was considered adequate in only two trials, both in cardiac surgery.<sup>13,18</sup> Most trials reported their eligibility criteria and had treatment groups with similar characteristics at baseline.

Four trials reported blinding of both patients and outcome assessors<sup>13,18,22,29</sup> and one was reported as an unblinded study;<sup>23</sup> the other trials were unclear with respect to blinding of one or both groups. Six trials reported results on an ITT basis.<sup>13,19,21-24</sup> *A priori* sample size calculations were reported for only four trials,<sup>13,17,18,23</sup> three of which were in cardiac surgery. Withdrawals and drop-outs were reported for most trials. With two exceptions,<sup>25,26</sup> trials that did not report withdrawals were focused on aspects other than effectiveness (cost-effectiveness<sup>13</sup> or pharmacokinetics<sup>27</sup>).

Overall, the included trials showed a wide range of variation in methodological quality as presented in their published reports. The two trials with the best quality ratings were both in cardiac surgery,<sup>13,18</sup> although one was a report of the economic analysis rather than the full trial results.<sup>13</sup> One trial in vascular surgery also scored well on most quality criteria.<sup>22</sup> Methodological aspects of the included trials in orthopaedic surgery were often poorly reported.

### Surgical site infection (SSI)

#### Within 30 days of surgery

Twelve trials reported the occurrence of an SSI within 30 days of surgery (or during postoperative hospitalisation if the trial did not define the timings of infections but the estimated overall duration of postoperative stay was approximately 30 days).<sup>17-26,28,29</sup> The results are presented in *Figure 3* and full details of all SSIs are presented in *Table 4*.

Only one trial found a statistically significant benefit of glycopeptide use. This was the trial of cardiac and vascular procedures by Maki and colleagues where fewer patients receiving vancomycin (3.7%) had infections than patients

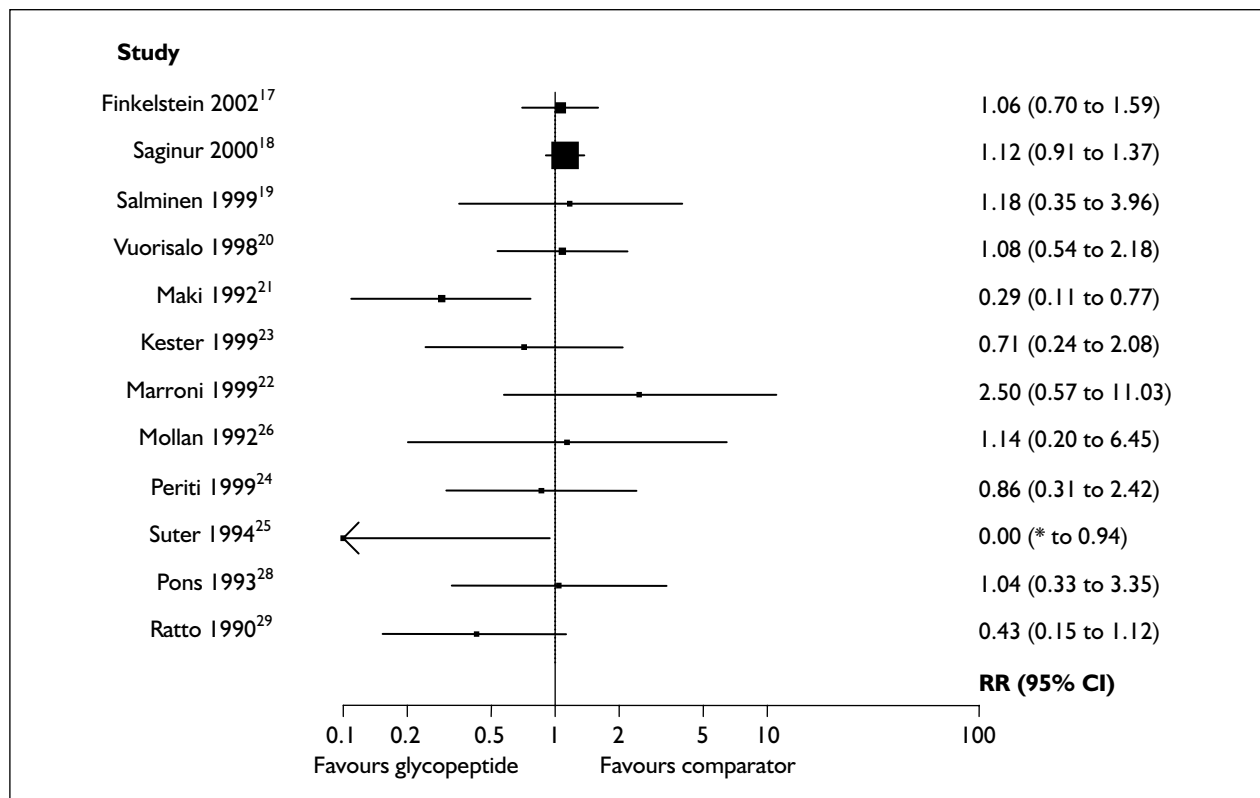


FIGURE 3 SSI within 30 days

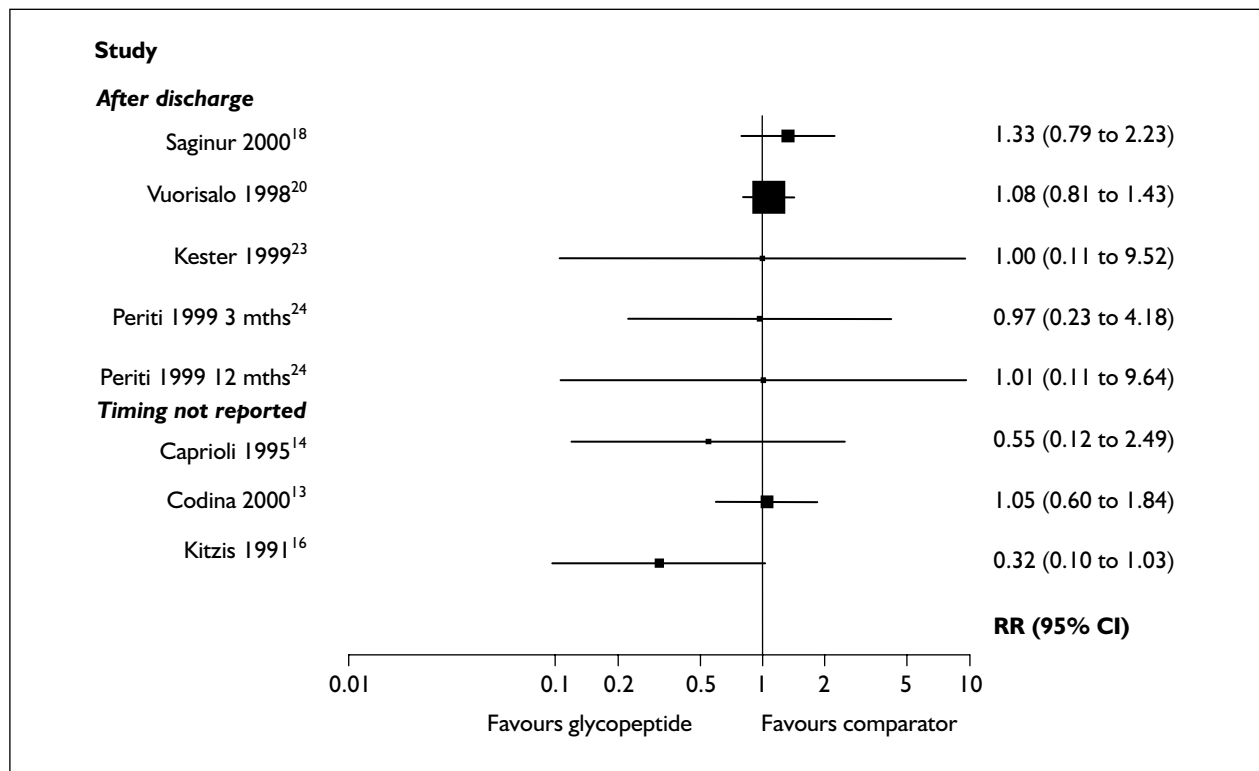
TABLE 4 Surgical site infections

Surgery	Study	Glycopeptide	n/N	Comparator	n/N
<b>SSI within 30 days</b>					
Cardiac	Finkelstein, 2002 <sup>17</sup>	Vancomycin	43/452	Cefazolin	39/433
	Saginur, 2000 <sup>18</sup>	Teicoplanin	174/1518	Cefazolin	155/1509
	Salminen, 1999 <sup>19</sup>	Vancomycin	5/103	Ceftriaxone	4/97
	Vuorisalo, 1998 <sup>20</sup>	Vancomycin	15/440	Cefuroxime	14/444
Cardiac/vascular	Maki, 1992 <sup>21</sup>	Vancomycin	4/107	Cefazolin or cefamandole	29/227
Vascular	Kester, 1999 <sup>23</sup>	Teicoplanin	5/136	Cefradine	7/136
	Marroni, 1999 <sup>22</sup>	Teicoplanin	5/119	Cefazolin	2/119
Orthopaedic	Mollan, 1992 <sup>26</sup> (infections occurring after 8–10 days)	Teicoplanin	2/308	Cefamandole	2/352
	Periti, 1999 <sup>24</sup>	Teicoplanin	6/422	Cefazolin	7/424
	Suter, 1994 <sup>25</sup>	Teicoplanin	0/250	Cefamandole	4/246
Neurosurgery	Pons, 1993 <sup>28</sup>	Vancomycin	5/404	Ceftizoxime	5/422
Thoracic	Ratto, 1990 <sup>29</sup>	Teicoplanin (long-term)	4/25	Teicoplanin (short-term)	9/24
<b>SSI after hospital discharge</b>					
Cardiac	Saginur, 2000 <sup>18</sup> (6 months post-surgery)	Teicoplanin	32/1518	Cefazolin	24/1509
	Vuorisalo, 1998 <sup>20</sup> (antibiotics prescribed for suspected infections 1 month after discharge)	Vancomycin	80/440	Cefuroxime	75/444
Vascular	Kester, 1999 <sup>23</sup> (bacteriologically proven infections up to 3 months post-surgery)	Teicoplanin	1/136	Cefradine	1/136
	Marroni, 1999 <sup>22</sup> (graft infections up to 3 months post-surgery)	Teicoplanin	2/119	Cefazolin	0/119
Orthopaedic	Periti, 1999 <sup>24</sup> (deep wound infections 3 months post-surgery)	Teicoplanin	3/375	Cefazolin	3/364
	Periti, 1999 <sup>24</sup> (deep wound infections 12 months post-surgery)	Teicoplanin	1/340	Cefazolin	1/343
<b>No details of SSI timing reported</b>					
Orthopaedic	Caprioli, 1995 <sup>14</sup>	Vancomycin	2/83	Cefamandole	4/91
Cardiac	Codina, 2000 <sup>13</sup>	Teicoplanin	22/250	Vancomycin	21/250
Vascular	Kitzis, 1991 <sup>16</sup>	Vancomycin	3/98	Cefamandole	10/104

receiving either cefazolin or cefamandole (12.8%) (RR 0.29, 95% CI 0.11 to 0.77).<sup>21</sup> The trial by Suter and colleagues of hip replacement surgery reported no SSIs for patients receiving teicoplanin and four (1.6%) in patients receiving cefamandole (Fisher's exact test  $p = 0.059$ , as reported by the authors; the estimated RR shown in *Figure 3* has not been reported because of the incomplete 95% CI caused by zero values).<sup>25</sup> No statistically significant differences between glycopeptide and cephalosporin prophylaxis in preventing SSIs were found in the other trials.

#### After hospital discharge

Five trials provided results for late SSIs occurring after discharge (*Figure 4*).<sup>18,20,22–24</sup> No statistically significant differences between glycopeptide and cephalosporin prophylaxis in preventing late infections were found in any of the trials. One vascular trial reported graft infections in two teicoplanin patients at 53 and 75 days after surgery (one was caused by MSSA) compared with no late infections in the cefazolin group.<sup>22</sup> One orthopaedic trial reported details of infections occurring at 3 and 12 months, with there being no



**FIGURE 4** SSI after discharge

significant difference between teicoplanin and cefazolin (three infections at 3 months and one at 12 months in each group).<sup>24</sup> Two other orthopaedic trials reported that no late infections occurred.<sup>25,27</sup>

Three trials<sup>13,14,16</sup> did not provide information on when the SSI occurred and these are presented separately in *Figure 4*. No statistically significant differences between glycopeptide and cephalosporin prophylaxis in preventing infections were found in these three trials.

## Bacteria causing SSI

### MRSA

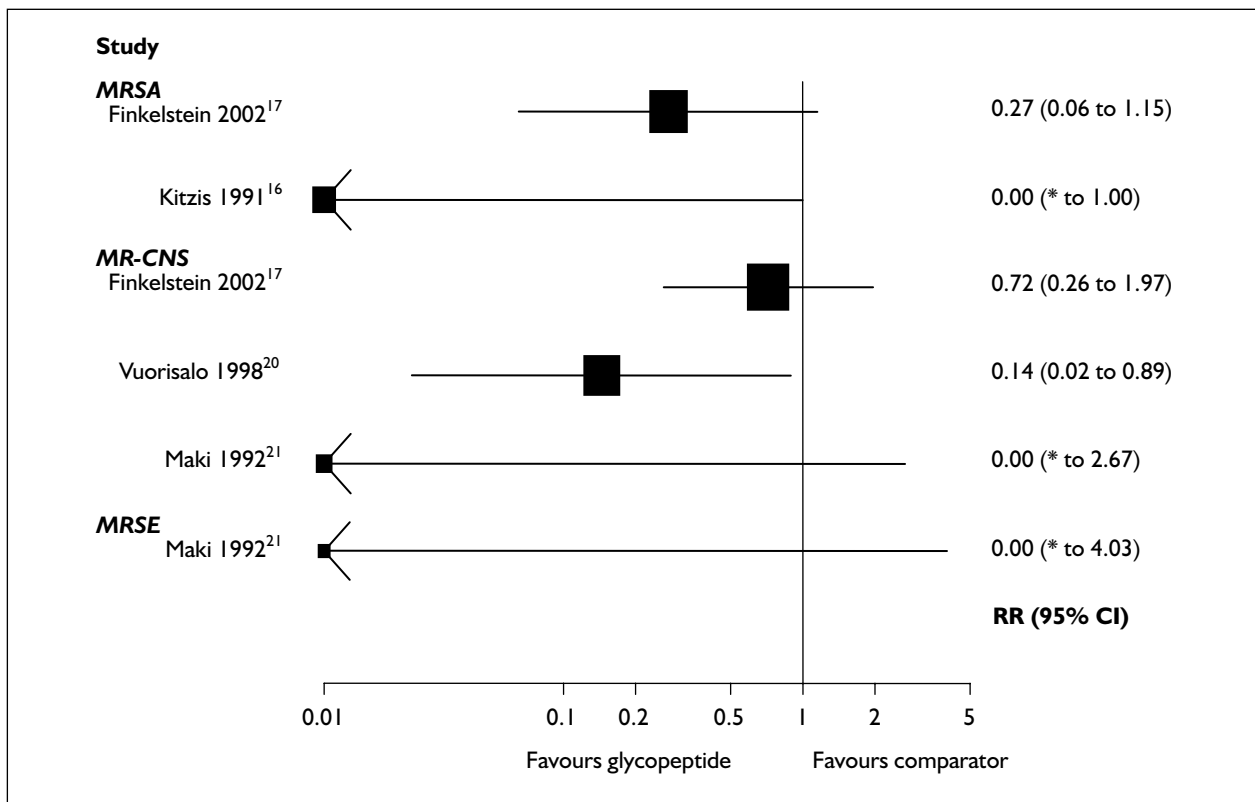
Two trials reported the numbers of SSIs caused by MRSA.<sup>16,17</sup> Three other trials reported that no MRSA infections occurred.<sup>19–21</sup> The trial of cardiac surgery by Saginur and colleagues reported that 50% of *S. epidermidis* and 6.1% of *S. aureus* strains isolated during the trial were resistant to methicillin but did not report these results by treatment group.<sup>18</sup> The remaining trials did not report whether they tested for MRSA. The results for infections caused by methicillin-resistant bacteria are presented in *Figure 5* and *Table 5*. The trial by Finkelstein and colleagues found fewer cases of MRSA infections in patients receiving vancomycin compared with cefazolin [two (0.4%)

and seven (1.6%), respectively], although this was not statistically significant.<sup>17</sup> This trial was conducted in a cardiac surgical ward with a high prevalence of MRSA infections (incidence of new cases of infection or colonisation in 1995 and 1996 of 3% and 2.6%, respectively). A trial of vascular surgery by Kitzis and colleagues reported no MRSA infections in vancomycin patients and four (3.8%) in patients receiving cefamandole.<sup>16</sup>

In addition to the trial by Finkelstein and colleagues,<sup>17</sup> a further three trials provided details of MRSA prevalence. One vascular trial reported that five (three CNS and two *S. aureus*) prosthetic vascular graft infections occurred in 298 procedures (1.7%) in 1994 and three of these were methicillin resistant.<sup>22</sup> One cardiac trial reported low prevalence but did not give any figures.<sup>18</sup> Another cardiac trial also reported low prevalence (0–0.4% from blood or pus specimens), with no new cases of MRSA occurring during the trial.<sup>20</sup>

### Other methicillin-resistant bacteria

Three trials reported the numbers of SSIs caused by methicillin-resistant coagulase-negative staphylococci (MR-CNS).<sup>17,20,21</sup> Patients receiving vancomycin [one (0.2%)] had significantly fewer MR-CNS infections compared with patients receiving cefuroxime [seven (1.6%)] in one trial of



**FIGURE 5** SSI caused by methicillin-resistant bacteria

cardiac surgery (RR 0.14, 95% CI 0.02 to 0.89).<sup>20</sup> No statistically significant differences between glycopeptide and cephalosporin prophylaxis were observed in the other two trials.

MRSE infections were reported in only one trial. One patient undergoing vascular surgery who received cefamandole in the trial by Maki and colleagues experienced a prosthetic graft infection caused by MRSE.<sup>21</sup> No MRSE infections occurred in the vancomycin group.

#### Glycopeptide-resistant bacteria

Two trials reported testing for resistance to glycopeptides.<sup>18,21</sup> The trial of cardiac surgery by Saginur and colleagues reported that no infections were resistant to teicoplanin, but 8% of the Gram-positive and 34% of the Gram-negative infections were resistant to cefazolin.<sup>18</sup> The trial of cardiac and vascular surgery by Maki and colleagues also reported that no infections were resistant to teicoplanin, but 20% of the Gram-positive and 60% of the Gram-negative infections were resistant to cefazolin or cefamandole.<sup>21</sup>

#### Gram-positive bacteria

Results for the total numbers of SSIs caused by Gram-positive bacteria (including all *S. aureus*, *S. epidermidis* and other CNS and CPS bacteria) are

presented in *Figure 6*. No statistically significant differences between glycopeptide and cephalosporin prophylaxis were observed in any of the trials. Only the trial of thoracic surgery by Ratto, which compared long-term to short-term teicoplanin prophylaxis in lung cancer patients undergoing pulmonary resection, found a statistically significant reduction in infections caused by Gram-positive bacteria for long-term teicoplanin prophylaxis (RR 0.21, 95% CI 0.06 to 0.76).<sup>29</sup>

#### Other bacteria

Results for the numbers of SSIs caused by other bacteria are presented in *Figure 7*. This includes infections caused by Gram-negative bacteria, anaerobes and polymicrobial infections (mixed Gram-positive and -negative bacteria). No statistically significant differences between glycopeptide and cephalosporin prophylaxis were observed in any of the trials.

#### Other infections

Details of other infections remote from the surgical site are presented in *Figures 8–10* and *Table 6*. Four trials reported the occurrence of bloodstream infections (*Figure 8*).<sup>17,18,21,22</sup> No statistically significant differences between glycopeptide and cephalosporin prophylaxis were observed in any of the trials.

TABLE 5 Bacteria causing SSI

Surgery	Study	Glycopeptide	n/N	Comparator	n/N
<b>MRSA</b>					
Cardiac	Finkelstein, 2002 <sup>17</sup>	Vancomycin	2/452	Cefazolin	7/433
Vascular	Kitzis, 1991 <sup>16</sup>	Vancomycin	0/98	Cefamandole	4/104
<b>MR-CNS</b>					
Cardiac	Finkelstein, 2002 <sup>17</sup>	Vancomycin	6/452	Cefazolin	8/433
	Vuorisalo, 1998 <sup>20</sup>	Vancomycin	1/440	Cefuroxime	7/444
Cardiac/vascular	Maki, 1992 <sup>21</sup>	Vancomycin	0/107	Cefamandole or cefazolin	3/227
<b>MRSE</b>					
Cardiac/vascular	Maki, 1992 <sup>21</sup>	Vancomycin	0/107	Cefamandole or cefazolin	1/227
<b>Gram-positive (total: including <i>S. aureus</i>, <i>S. epidermidis</i> and other CNS and CPS)</b>					
Cardiac	Finkelstein, 2002 <sup>17</sup>	Vancomycin	26/452	Cefazolin	26/433
	Saginur, 2000 <sup>18</sup>	Teicoplanin	83/1518	Cefazolin	60/1509
	Salminen, 1999 <sup>19</sup>	Vancomycin	3/103	Ceftriaxone	2/97
	Vuorisalo, 1998 <sup>20</sup>	Vancomycin	11/440	Cefuroxime	14/444
Cardiac/vascular	Maki, 1992 <sup>21</sup>	Vancomycin	2/107	Cefazolin	15/227
Vascular	Kester, 1999 <sup>23</sup>	Teicoplanin	2/136	Cefradine	2/136
	Marroni, 1999 <sup>22</sup>	Teicoplanin	0/119	Cefazolin	1/119
	Kitzis, 1991 <sup>16</sup>	Vancomycin	1/98	Cefamandole	4/104
Orthopaedic	Mollan, 1992 <sup>26</sup>	Teicoplanin	2/308	Cefamandole	2/352
	Periti, 1999 <sup>24</sup>	Teicoplanin	3/422	Cefazolin	4/424
	Suter, 1994 <sup>25</sup>	Teicoplanin	0/250	Cefamandole	4/246
Neurosurgery	Pons, 1993 <sup>28</sup>	Vancomycin	2/404	Ceftizoxime	4/422
Thoracic	Ratto, 1990 <sup>29</sup>	Teicoplanin (long-term)	2/25	Teicoplanin (short-term)	9/24
<b>Other bacteria (total: including Gram-negative, polymicrobial and anaerobic infections)</b>					
Cardiac	Finkelstein, 2002 <sup>17</sup>	Vancomycin	21/452	Cefazolin	20/433
	Saginur, 2000 <sup>18</sup>	Teicoplanin	21/1518	Cefazolin	27/1509
	Salminen, 1999 <sup>19</sup>	Vancomycin	1/103	Ceftriaxone	1/97
	Vuorisalo, 1998 <sup>20</sup>	Vancomycin	2/440	Cefuroxime	0/444
Cardiac/vascular	Maki, 1992 <sup>21</sup>	Vancomycin	0/107	Cefazolin	5/227
Vascular	Kester, 1999 <sup>23</sup>	Teicoplanin	4/136	Cefradine	6/136
	Marroni, 1999 <sup>22</sup>	Teicoplanin	2/119	Cefazolin	1/119
	Kitzis, 1991 <sup>16</sup>	Vancomycin	2/98	Cefamandole	6/104
Orthopaedic	Periti, 1999 <sup>24</sup>	Teicoplanin	1/422	Cefazolin	2/424
Thoracic	Ratto, 1990 <sup>29</sup>	Teicoplanin (long-term)	2/25	Teicoplanin (short-term)	0/24

Ten trials reported the occurrence of respiratory tract infections (Figure 9).<sup>14,18,19,21-25,28,29</sup> The trial of cardiac surgery by Saginur and colleagues reported significantly more respiratory tract infections in the teicoplanin patients (7.6%) than in the cefazolin patients (4.7%) (RR 1.62, 95% CI 1.22 to 2.16).<sup>18</sup>

Eight trials reported the occurrence of urinary tract infections (Figure 10).<sup>14,18,19,21,22,24,25,28</sup> The trial by Saginur and colleagues was again the only trial to observe a statistically significant difference

between a glycopeptide and a cephalosporin with more teicoplanin patients (7.5%) than cefazolin patients (1.8%) (RR 4.2, 95% CI 2.79 to 6.33) experiencing a urinary tract infection.<sup>18</sup>

### Bacteria causing other infections

In the trial of cardiac surgery by Finkelstein and colleagues,<sup>17</sup> MRSA was isolated in the bloodstream infections of two (0.4%) vancomycin patients and four (0.9%) cefazolin patients, and MR-CNS was isolated in two (0.4%) vancomycin patients and two (0.5%) cefazolin patients. In the



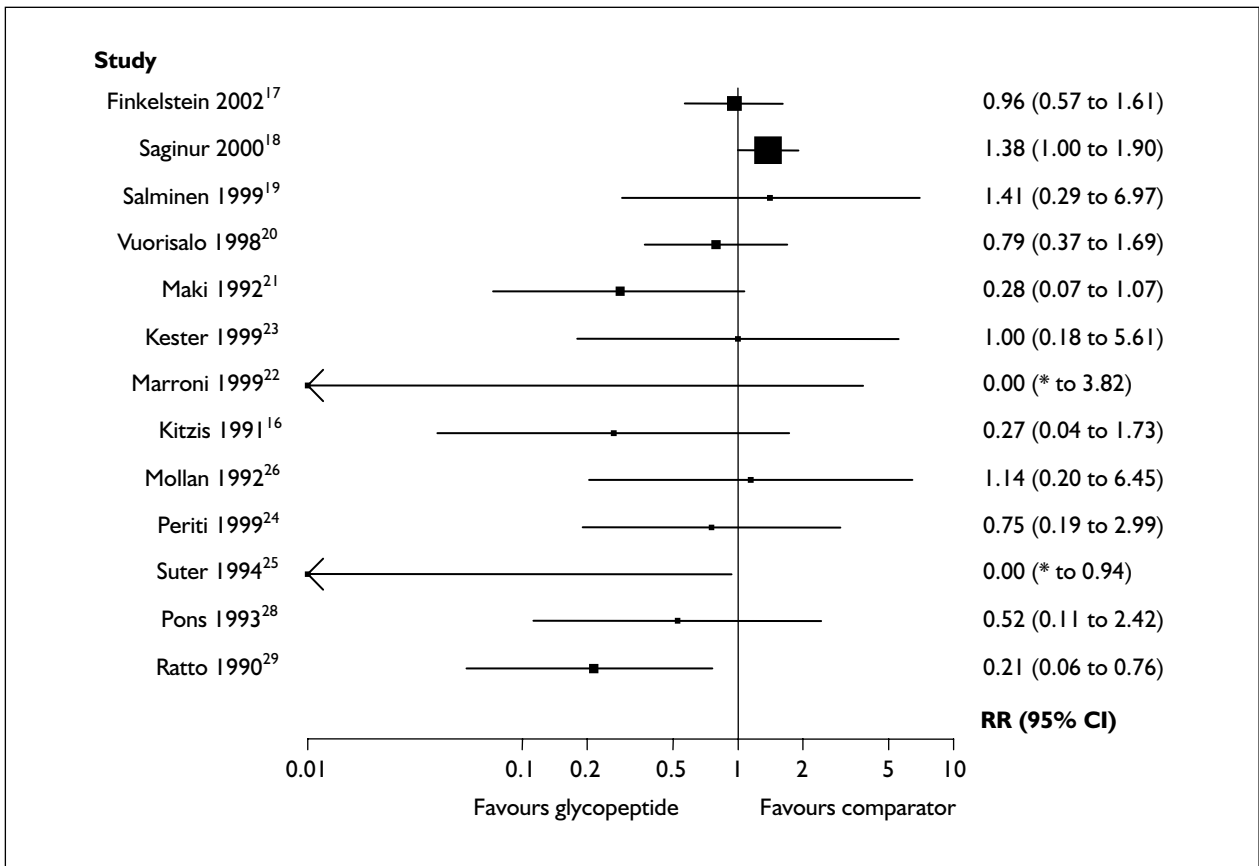


FIGURE 6 SSI caused by Gram-positive bacteria

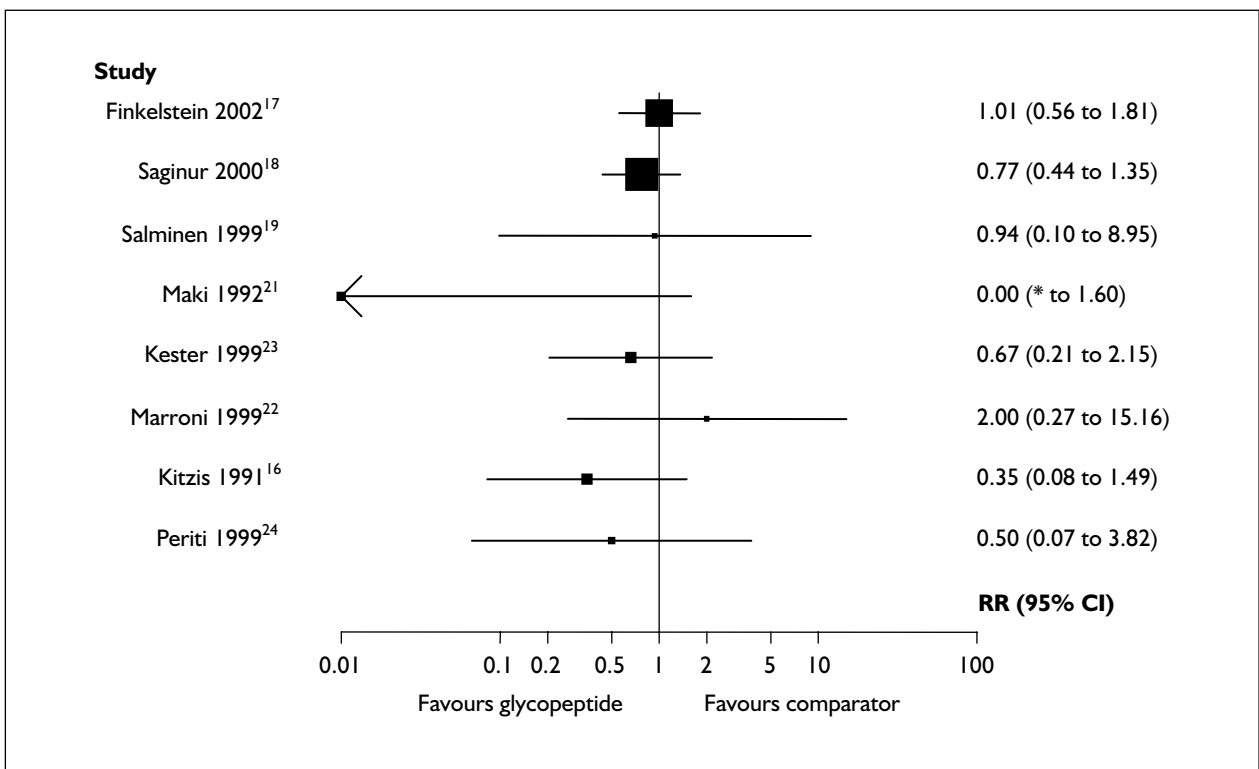


FIGURE 7 SSI caused by other bacteria

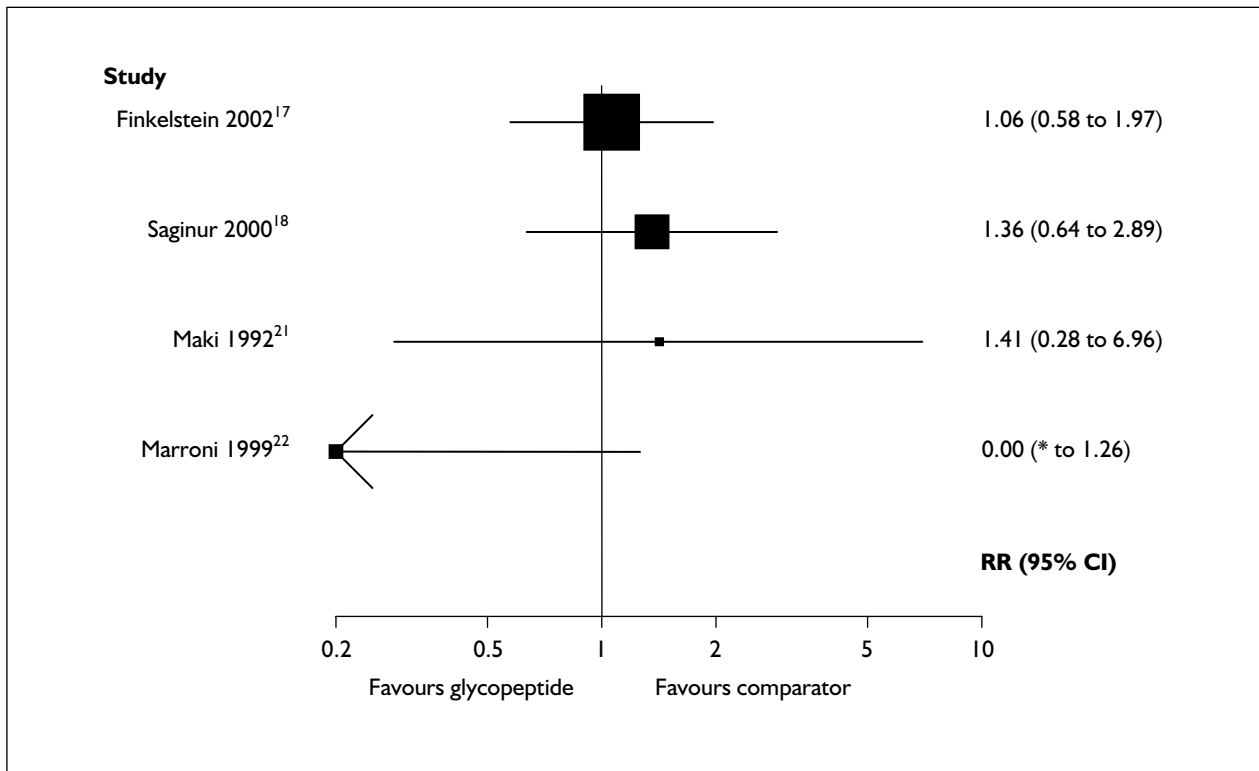


FIGURE 8 Bloodstream infections

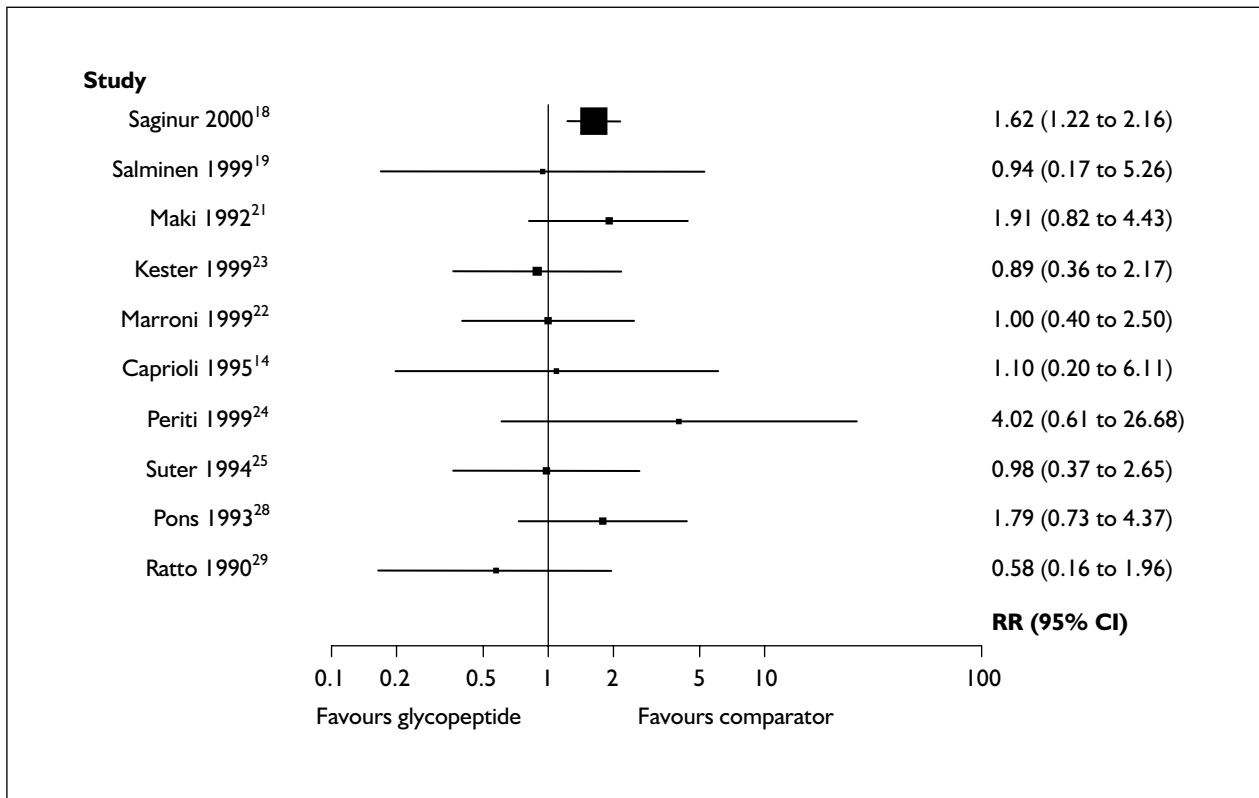


FIGURE 9 Respiratory tract infections

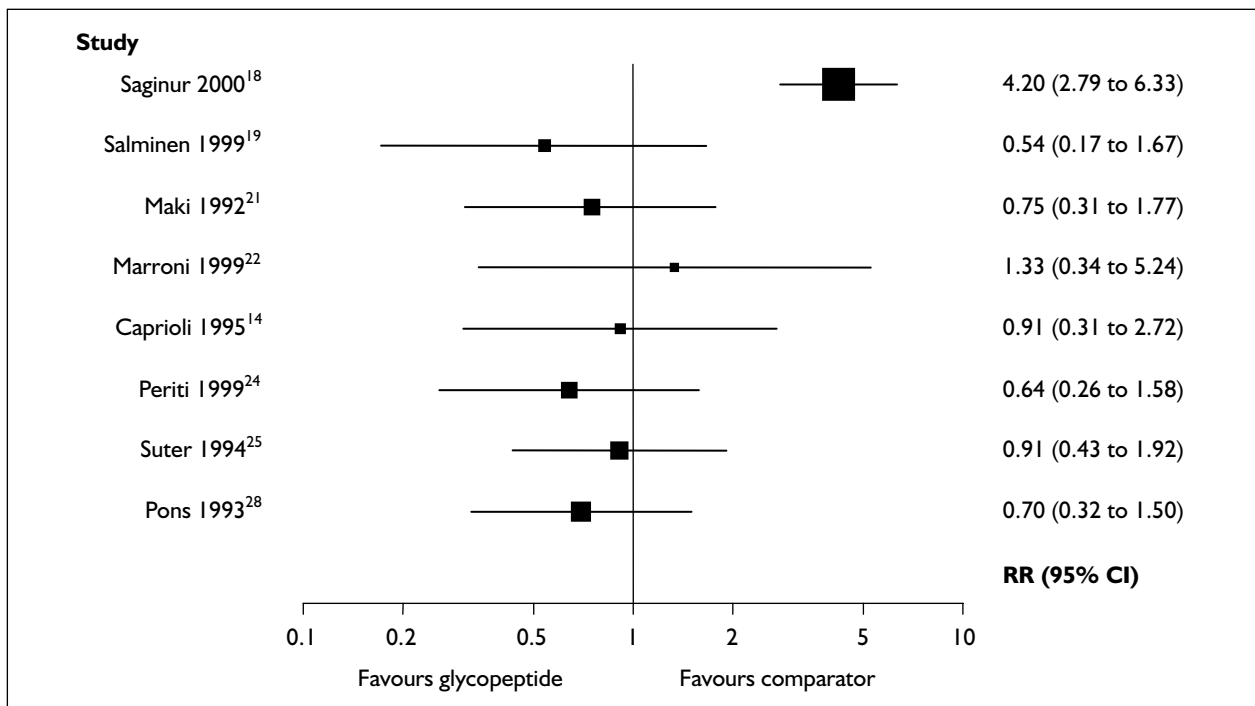


FIGURE 10 Urinary tract infections

TABLE 6 Other infections

Surgery	Study	Glycopeptide	n/N	Comparator	n/N
<b>Bloodstream</b>					
Cardiac	Finkelstein, 2002 <sup>17</sup>	Vancomycin	20/452	Cefazolin	18/433
	Saginur, 2000 <sup>18</sup>	Teicoplanin	15/1518	Cefazolin	11/1509
Cardiac/vascular	Maki, 1992 <sup>21</sup>	Vancomycin	2/107	Cefazolin	3/227
Vascular	Marroni, 1999 <sup>22</sup>	Teicoplanin	0/119	Cefazolin	3/119
<b>Respiratory tract</b>					
Cardiac	Saginur, 2000 <sup>18</sup>	Teicoplanin	116/1518	Cefazolin	71/1509
	Salminen, 1999 <sup>19</sup> (at 7 days)	Vancomycin	2/103	Ceftriaxone	2/97
Cardiac/vascular	Maki, 1992 <sup>21</sup>	Vancomycin	9/107	Cefazolin	10/227
Vascular	Kester, 1999 <sup>23</sup>	Teicoplanin	8/136	Cefradine	9/136
	Marroni, 1999 <sup>22</sup> (pneumonia)	Teicoplanin	8/119	Cefazolin	8/119
Orthopaedic	Caprioli, 1995 <sup>14</sup> (pneumonia/pleuritis)	Vancomycin	2/83	Cefamandole	2/91
	Periti, 1999 <sup>24</sup>	Teicoplanin	4/422	Cefazolin	1/424
	Suter, 1994 <sup>25</sup>	Teicoplanin	7/250	Cefamandole	7/246
Neurosurgery	Pons, 1993 <sup>28</sup> (pneumonia)	Vancomycin	12/404	Ceftizoxime	7/422
Thoracic	Ratto, 1990 <sup>29</sup>	Teicoplanin (long-term)	3/25	Teicoplanin (short-term)	5/24
<b>Urinary tract</b>					
Cardiac	Saginur, 2000 <sup>18</sup>	Teicoplanin	114/1518	Cefazolin	27/1509
	Salminen, 1999 <sup>19</sup>	Vancomycin	4/103	Ceftriaxone	7/97
Cardiac/vascular	Maki, 1992 <sup>21</sup>	Vancomycin	6/107	Cefazolin	17/227
Vascular	Marroni, 1999 <sup>22</sup>	Teicoplanin	4/119	Cefazolin	3/119
Orthopaedic	Caprioli, 1995 <sup>14</sup>	Vancomycin	5/83	Cefamandole	6/91
	Periti, 1999 <sup>24</sup> (UTI + bacteriuria)	Teicoplanin	7/422	Cefazolin	11/424
	Suter, 1994 <sup>25</sup>	Teicoplanin	12/250	Cefamandole	13/246
Neurosurgery	Pons, 1993 <sup>28</sup>	Vancomycin	10/404	Ceftizoxime	15/422

UTI, urinary tract infection.

trial of cardiac and vascular surgery by Maki and colleagues,<sup>21</sup> none of the remote infections were caused by MRSA and two (1.8%) of the cefamandole patients and none of the vancomycin patients had remote infections caused by MR-CNS. None of the other trials reported the bacteriology of remote infections.

**Mortality**

Six trials<sup>17,18,20,22,25,29</sup> reported deaths from any cause (Figure 11 and Table 7) and four trials<sup>18,20,22,23</sup> reported deaths that were caused by or related to an infection (Figure 12 and Table 7). No statistically significant differences between glycopeptide and cephalosporin prophylaxis were observed in any of the trials and the numbers of infection-related deaths were generally small. In the trial of vascular surgery by Marroni and colleagues, one teicoplanin patient died from a prosthesis related infection and one cefazolin patient died from a bloodstream infection.<sup>22</sup> In the two cardiac surgery trials, Saginur and colleagues reported that 14 (0.9%) teicoplanin and 12 (0.8%) cefazolin patients had ongoing infections at the time of death;<sup>18</sup> and Vuorisalo and colleagues reported no infection-related deaths amongst patients receiving vancomycin but one cefuroxime patient died from mediastinitis caused by MR-CNS.<sup>20</sup>

**Length of postoperative stay**

Seven trials reported the length of postoperative hospital stay (Figure 13 and Table 8).<sup>17,18,20,21,23-25</sup>

Two trials reported the mean length of stay but not the associated standard deviation (SD) and are not included in Figure 13. The trial by Maki and colleagues was the only trial to report a statistically significant difference between the glycopeptide and cephalosporin arms.<sup>21</sup> Patients receiving vancomycin stayed in hospital for less time than those receiving either cefazolin or cefamandole (mean difference 1.9 days, 95% CI 0.2 to 3.5 days).

**Rehospitalisation and reoperation**

Only one trial, of cardiac surgery by Saginur and colleagues, reported the incidence of rehospitalisation.<sup>18</sup> A total of 320 (21.1%) teicoplanin and 297 (19.7%) cefazolin patients were rehospitalised after surgery and 52 (3.4%) teicoplanin and 42 cefazolin (2.8%) patients underwent repeat surgery. It was not reported if any of these were related to an infection.

**Morbidity**

There were no reports of cases of morbidity or disability related to infections.

**Adverse events**

Nine studies included in the effectiveness review reported on AEs possibly or probably related to antibiotic prophylaxis.<sup>13,18,21,23-26,28,29</sup> Of these, one study compared vancomycin with teicoplanin<sup>13</sup> and one compared long-term and short-term teicoplanin prophylaxis.<sup>29</sup> Three studies were included in the review for data on

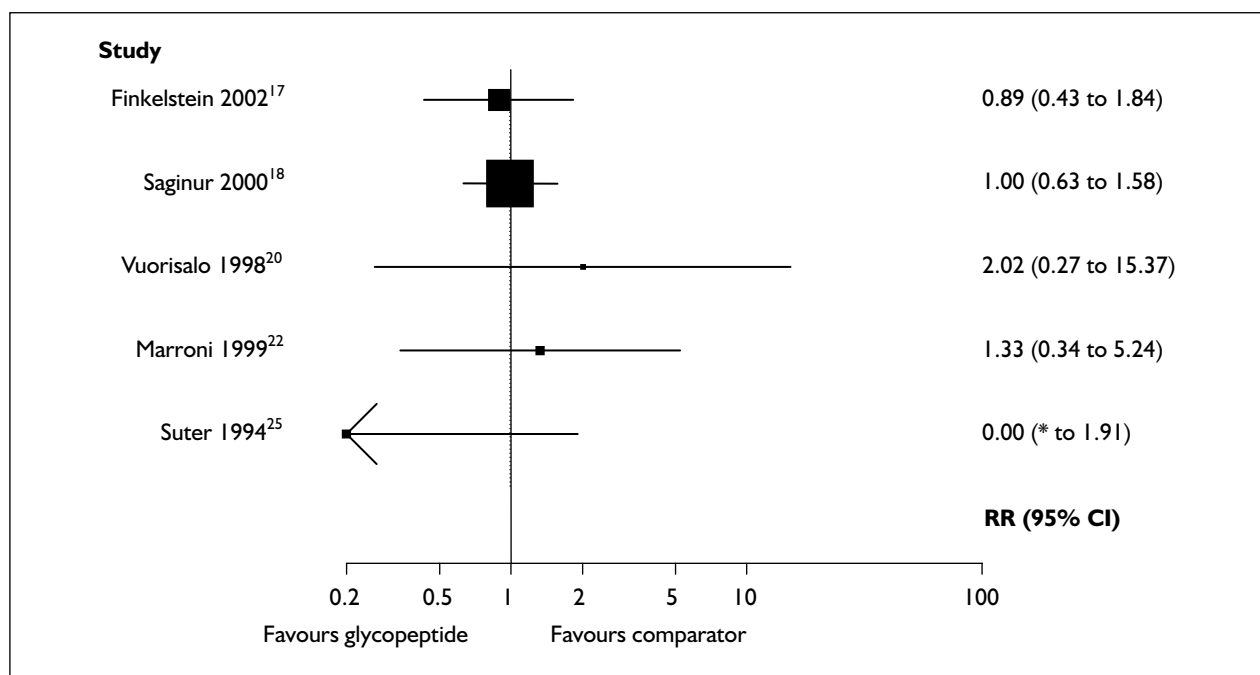


FIGURE 11 Death from any cause

AEs only.<sup>15,30,31</sup> One study compared vancomycin with cefamandole (both with or without aprotinin),<sup>30</sup> although its aim was to assess the effect of these drugs on kidney function. Miro and colleagues reported adverse events from an open, non-randomised study comparing patients undergoing CABG or valve replacement from 1992 to 1994 who received teicoplanin prophylaxis with patients from 1990 to 1992 who received vancomycin.<sup>15</sup> Romanelli and colleagues randomised patients undergoing CABG to vancomycin or placebo (in addition to cefazolin) to

assess the haemodynamic effects of vancomycin administration.<sup>31</sup> All AE data are summarised in *Table 9*.

'Red man syndrome' is an adverse reaction to vancomycin often attributed to rapid drug infusion, with symptoms including hypotension, pruritis and flushing of the face, neck and upper torso. Six studies reported the occurrence of hypotension or red man syndrome after vancomycin administration, with the numbers of patients affected ranging from 0.2 to 50%. Two

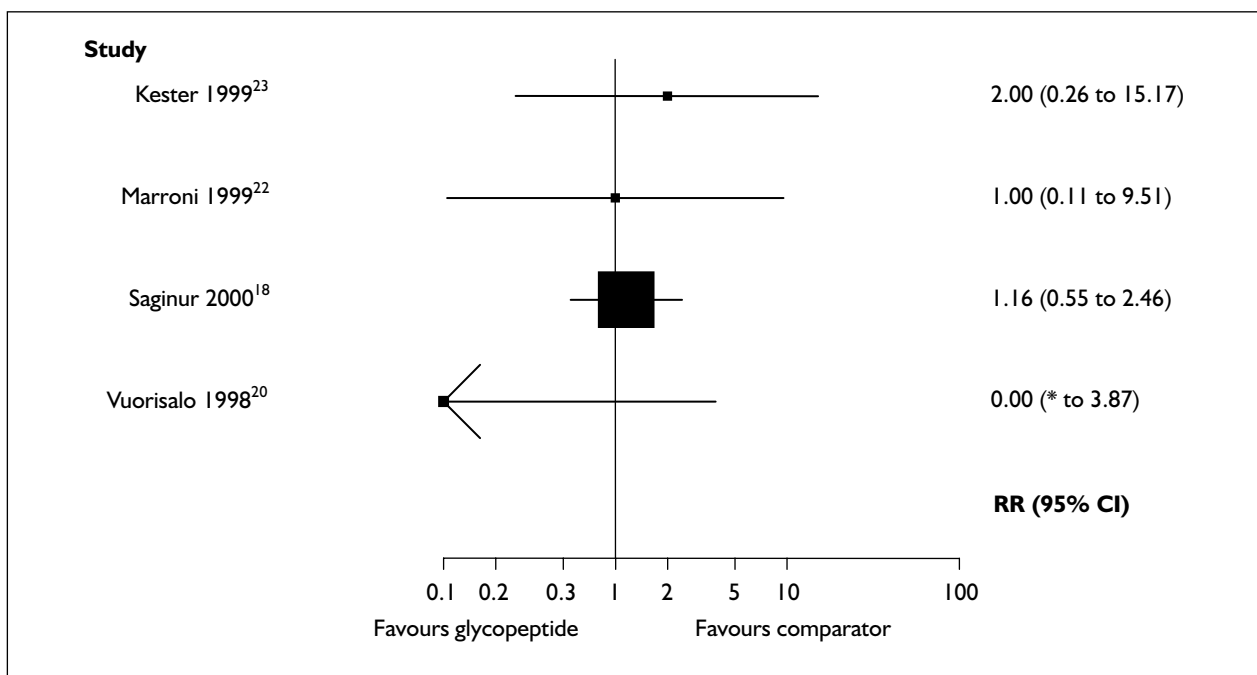


FIGURE 12 Death relating to infection

TABLE 7 Mortality

Surgery	Study	Glycopeptide	n/N	Comparator	n/N
<b>Death from any cause</b>					
Cardiac	Finkelstein, 2002 <sup>17</sup>	Vancomycin	13/452	Cefazolin	14/433
	Saginur, 2000 <sup>18</sup>	Teicoplanin	35/1527	Cefazolin	35/1520
	Vuorisalo, 1998 <sup>20</sup>	Vancomycin	2/440	Cefuroxime	1/444
Vascular	Marroni, 1999 <sup>22</sup>	Teicoplanin	4/119	Cefazolin	3/119
Orthopaedic	Suter, 1994 <sup>25</sup>	Teicoplanin	0/260	Cefamandole	2/260
Thoracic	Ratto, 1990 <sup>29</sup>	Teicoplanin (long-term)	1/25	Teicoplanin (short-term)	0/24
<b>Death relating to infection</b>					
Vascular	Kester, 1999 <sup>23</sup>	Teicoplanin	2/136	Cefradine	1/136
	Marroni, 1999 <sup>22</sup>	Teicoplanin	1/119	Cefazolin	1/119
Cardiac	Saginur, 2000 <sup>18</sup>	Teicoplanin	14/1527	Cefazolin	12/1520
	Vuorisalo, 1998 <sup>20</sup>	Vancomycin	0/440	Cefuroxime	1/444

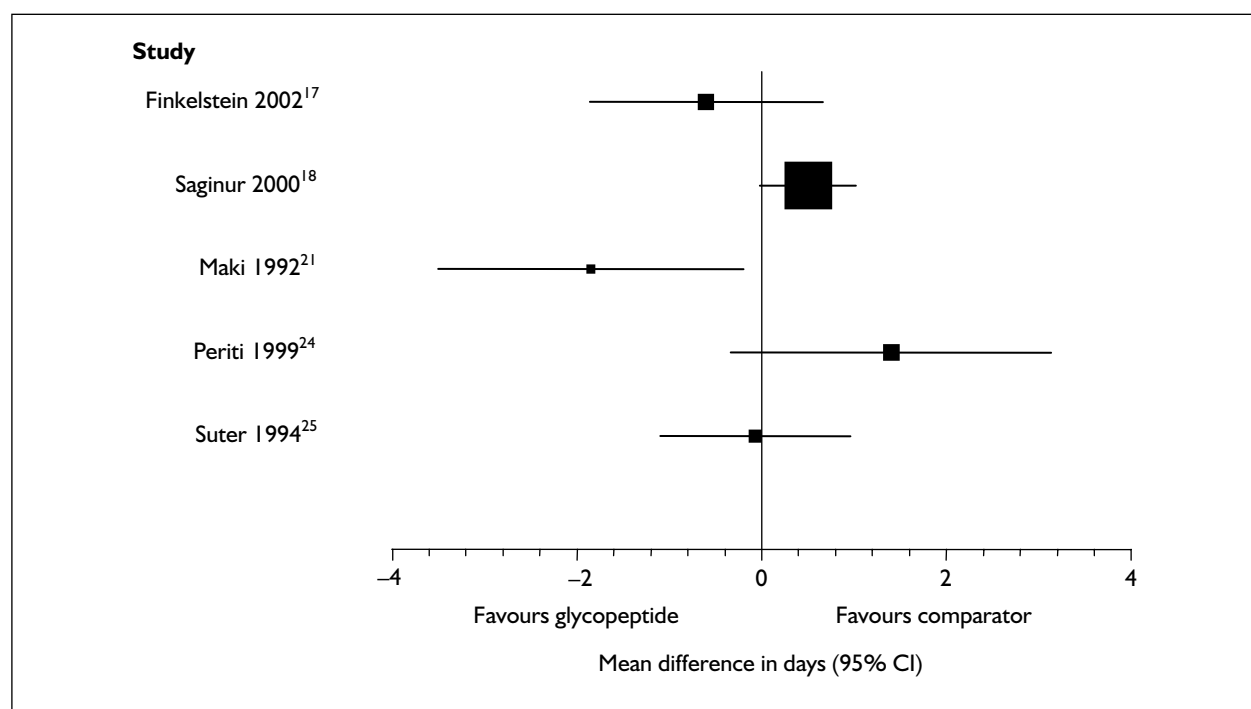


FIGURE 13 Length of postoperative stay

TABLE 8 Length of postoperative stay (days)

Surgery	Study	Glycopeptide	Mean	SD	Comparator	Mean	SD
Cardiac	Finkelstein, 2002 <sup>17</sup>	Vancomycin	8.7	8	Cefazolin	9.3	11
	Saginur, 2000 <sup>18</sup>	Teicoplanin	10	7.9	Cefazolin	9.5	6.7
	Vuorisalo, 1998 <sup>20</sup>	Vancomycin	11	NR	Cefuroxime	11	NR
Cardiac/vascular	Maki, 1992 <sup>21</sup>	Vancomycin	10.1	6.1	Cefazolin or cefamandole	12	7.63
Vascular	Kester, 1999 <sup>23</sup>	Teicoplanin	15.4	NR	Cefradine	20.8	NR
Orthopaedic	Periti, 1999 <sup>24</sup>	Teicoplanin	24.4	13.7	Cefazolin	23	12
	Suter, 1994 <sup>25</sup>	Teicoplanin	17.04	6.55	Cefamandole	17.11	5.02

NR, not reported.

studies reported red man syndrome, which occurred in 1.5% (6/404) of vancomycin patients compared with no ceftizoxime patients in one study,<sup>28</sup> and 5% (37/736) of vancomycin patients compared with 1.1% (7/656) of teicoplanin patients in the other study.<sup>15</sup>

Four studies reported on hypotension with serious hypotension in one study (defined by the study as a reduction in systolic arterial pressure greater than 30%) occurring in one patient (0.4%) in each of the vancomycin and teicoplanin groups.<sup>13</sup> In a second study, hypotension during drug administration (pre- or postoperative) occurred in 7.5% (8/107) of vancomycin compared with 2.2%

(5/227) of control patients (receiving cefamandole or cefazolin); this resolved in most patients when infusion was stopped and resumed at a lower rate but three vancomycin and two control patients were removed from the trial.<sup>21</sup> Hypotension requiring a norepinephrine infusion occurred in 5% (37/736) of vancomycin plus cefazolin patients compared with 14.3% (4/28) of cefazolin patients in a third study, although the aim of this study was to assess the haemodynamic effects of drug infusion, not its prophylactic effectiveness.<sup>31</sup> One teicoplanin study also reported hypotension, which occurred in three teicoplanin patients (0.2%) compared with five (0.3%) cefazolin patients.<sup>18</sup>

**TABLE 9** Adverse events possibly or probably related to antibiotic prophylaxis

Study	Adverse event	Glycopeptide	n/N	Comparator	n/N
<b>Studies included for effectiveness</b>					
Codina, 2000 <sup>13</sup>	AE after first dose	Vancomycin	51/250	Teicoplanin	4/250
	AE after second dose	Vancomycin	6/118	Teicoplanin	1/115
	Hypotension (considered serious)	Vancomycin	1/250	Teicoplanin	1/250
Kester, 1999 <sup>23</sup>	Event possibly or probably related to drug	Teicoplanin	19/136	Cefradine	15/136
Maki, 1992 <sup>21</sup>	<i>C. difficile</i> antibiotic-associated colitis (mild)	Vancomycin	0/107	Cefamandole/cefazolin	2/227
	Maculopapular rash (mild)	Vancomycin	1/107	Cefamandole/cefazolin	3/227
	Hypotension during administration (pre- or post-operative)	Vancomycin	8/107	Cefamandole/cefazolin	5/227
	Patient removed from study due to hypotension	Vancomycin	3/107	Cefamandole/cefazolin	2/227
Mollan, 1992 <sup>26</sup>	Vomiting <sup>a</sup>	Teicoplanin	1/394	Cefamandole	1/407
	Pruritis/flushing	Teicoplanin	0/394	Cefamandole	1/407
Periti, 1999 <sup>24</sup>	Erythema	Teicoplanin	0/394	Cefazolin	1/424
	Rash	Teicoplanin	0/394	Cefazolin	1/424
Pons, 1993 <sup>28</sup>	Red man syndrome (hypotension and/or flushing)	Vancomycin	6/404	Ceftizoxime	0/422
Ratto, 1990 <sup>29</sup>	Postoperative diarrhoea	Teicoplanin (long-term)	3/25	Teicoplanin (short-term)	1/24
Saginur, 2000 <sup>18</sup>	Anaphylactic shock	Teicoplanin	1/1518	Cefazolin	1/1509
	Hypotension	Teicoplanin	3/1518	Cefazolin	5/1509
	Nausea	Teicoplanin	30/1518	Cefazolin	22/1509
	Rash	Teicoplanin	4/1518	Cefazolin	3/1509
	Vomiting	Teicoplanin	12/1518	Cefazolin	11/1509
Suter, 1994 <sup>25</sup>	Allergic reaction after first injection	Teicoplanin	1/260	Cefamandole	2/260
<b>Studies included for adverse events only</b>					
Mercieri, 1999 <sup>30</sup>	Acute renal failure (no dialysis required)	Vancomycin	0/21	Cefamandole	1/18
	Acute renal failure (no dialysis required)	Vancomycin (plus aprotinin)	1/23	Cefamandole (plus aprotinin)	0/22
Miro, 1996 <sup>15</sup>	Severe hypotension/red man syndrome	Vancomycin	37/736	Teicoplanin	7/656
Romanelli, 1993 <sup>31</sup>	Hypotension requiring a norepinephrine infusion	Vancomycin (plus cefazolin)	15/30	Cefazolin	4/28

<sup>a</sup> Teicoplanin patient had vomiting and erythema.

Other AEs reported were generally mild and included nausea, vomiting and rash. In general, rates of these were low and similar between glycopeptide and comparator groups. One study that reported a higher rate of events in the vancomycin arm (20.4% of patients after the first dose) found a higher incidence of AEs after the both the first and second doses compared with teicoplanin (1.6%), although these were not

considered to be serious and were mainly erythema and pruritis.<sup>13</sup>

## Discussion

Only one trial of cardiac and vascular surgery found a statistically significant reduction in the numbers of SSIs occurring within 30 days of

surgery for patients receiving vancomycin compared with cefazolin or cefamandole.<sup>21</sup> Most of the trials did not report MRSA infections: two trials provided results for the numbers of infections caused by MRSA; three trials reported that no MRSA infections occurred; and one trial reported the number of MRSA infections overall but not separately for the glycopeptide and comparator groups. Both trials that provided MRSA results reported fewer MRSA infections in the glycopeptide arm but the results were not statistically significant. One of these was the only trial to report both MRSA prevalence and MRSA infections and was conducted in a cardiac unit with a high MRSA prevalence.<sup>17</sup> Only one trial reported the occurrence of infections caused by MRSE. There was a limited amount of evidence that glycopeptide prophylaxis might be more effective in preventing infections caused by methicillin-resistant bacteria (including MRSA, MR-CNS and MRSE) with fewer infections reported in the glycopeptide arms of four trials, although this was only statistically significant in one trial.<sup>21</sup>

With the exception of one trial,<sup>17</sup> the prevention of MRSA infections was not the primary objective and most did not report the baseline prevalence of MRSA. This confirms the findings of the review by Bolon and colleagues which found no evidence to support a switch from beta-lactams to glycopeptide prophylaxis in cardiac surgery.<sup>32</sup> Only two trials reported testing for glycopeptide-resistance and both found no resistance to teicoplanin.

Many of the trials included in the effectiveness review had weaknesses in design and/or reporting. Very few reported an *a priori* sample size calculation and so were likely to have been under-powered for detecting a difference in SSI rates. The largest and best conducted trial was in cardiac surgery,<sup>18</sup> but this did not provide any comparative results for MRSA infections or report prevalence (other than saying it was low). Poor reporting may reflect the fact that many of these trials were published before the CONSORT standards for reporting of RCTs were widely adopted.<sup>33</sup> Follow-up beyond 12 months was rarely reported, which may be an issue for orthopaedic surgery, where deep infections occurring some time after surgery are a major concern.

Most trials gave antibiotics at induction of anaesthesia, although some were earlier. Typical

doses were 1 g for vancomycin, 400 mg for teicoplanin and 1 or 2 g for cephalosporin comparators. Overall, there was not enough evidence to judge whether different doses and/or durations affected the risk of developing an infection. None of the trials evaluated the effect of varying dose or time of administration. There was also limited information on the effects of single compared with combined antibiotic regimens (no direct comparisons). Two orthopaedic trials assessed a glycopeptide plus gentamicin (alone or in bone cement), a neurosurgery trial assessed vancomycin plus gentamicin and one cardiac trial assessed vancomycin plus netilmicin.

The most common comparators (four trials each) were cefazolin and cefamandole. Third-generation cephalosporins were used as comparators in only two trials. Only one trial compared a glycopeptide with two different cephalosporins and the results for SSIs were similar for each cephalosporin.<sup>21</sup>

Most trials in the effectiveness review reported AEs and three additional studies were included for AEs only. The AE rates were generally low and most were mild such as nausea and vomiting. More serious events such as red man syndrome or serious hypotension were more common with vancomycin in four of the five studies that reported their occurrence. AEs were more frequent with vancomycin than with teicoplanin in direct comparisons.<sup>13,15</sup> Any increase in infection prophylaxis from a switch to vancomycin from cephalosporins needs to be balanced against an increased risk of AEs.

## Summary

The systematic review of effectiveness found that there was insufficient evidence available to suggest a threshold level of MRSA prevalence at which it would be appropriate to switch from non-glycopeptide to glycopeptide antibiotics for surgical infection prophylaxis. There was also a lack of evidence from RCTs to conclude that glycopeptide regimens are more effective than non-glycopeptides in preventing SSIs. Most studies did not test for drug-resistant bacteria, so the effectiveness review is unable to provide any information about the risk of increasing bacterial resistance to glycopeptides.



# Chapter 4

## Systematic review of cost-effectiveness

### Methods

The aim of the systematic review of published economic evaluations was to examine the cost-effectiveness of glycopeptide antibiotics compared with appropriate comparators.

### Search strategy

The literature searches for this review were undertaken in the same databases used for the effectiveness review (see Chapter 3).

Additional searches of the following economics databases were also undertaken (the search strategy is presented in Appendix 1):

- NHS EED
- HEED
- IDEAS.

### Inclusion criteria

Studies that were full economic evaluations were considered, that is: (1) cost-effectiveness evaluations, including cost-minimisation and cost-consequence analyses; (2) cost-utility analyses; and (3) cost-benefit analyses.<sup>34</sup> At least one of the interventions had to be a glycopeptide used as antibiotic prophylaxis for surgery.

### Data extraction and quality assessment

Data were extracted on key components of standard economic evaluations, including data on the comparators, study population, main analytic approaches (e.g. patient-level analysis/decision analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality of life, direct costs (medical and non-medical) and productivity costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic/probabilistic sensitivity analysis). Additional data were captured on whether or not screening and/or diagnostic tests for bacterial colonisation were undertaken, the type of surgery, the surgical site, the surgical environment, the method of administration of the prophylaxis, the use of other interventions to prevent/reduce infection rate and methods used to assess antibiotic resistance).

The quality of the cost-effectiveness studies was assessed according to a list updated from that developed by Drummond and colleagues.<sup>34</sup> The list of items indicated components of 'good quality' in a standardised manner (see Appendix 2).

### Results

#### Nature of the evidence

Fourteen potential studies were identified from the search of the NHS EED database. No additional studies were identified from other economic databases or the searches for the clinical effectiveness review. Once the inclusion/exclusion criteria were applied, five relevant cost-effectiveness studies of glycopeptide antibiotic prophylaxis were included.<sup>13,22,35-37</sup> All studies focused on clean surgery with the exception of that by Phillips and colleagues.<sup>35</sup> Surgical sites covered were cardiac,<sup>13,36</sup> cardiothoracic,<sup>37</sup> prosthetic vascular<sup>22</sup> and cardiovascular.<sup>35</sup> The full data extraction tables are presented in Appendix 5 and the quality assessment in Appendix 6.

Glycopeptides (teicoplanin or vancomycin) were compared with each other or with cefazolin. No studies compared all glycopeptide and non-glycopeptide antibiotic prophylaxis which are relevant to this review. The following antibiotics were compared: vancomycin versus teicoplanin,<sup>13</sup> teicoplanin versus cefazolin,<sup>22</sup> vancomycin versus cefazolin<sup>35,37</sup> and vancomycin and rifampicin versus cefazolin.<sup>36</sup>

Glycopeptides were administered at induction of anaesthesia as single doses [coronary artery bypass graft (CABG) arm<sup>13,22</sup>] or perioperatively as multiple doses [in the valve replacement (VR) arm<sup>13,35-37</sup>]. The duration of time over which multiple doses were administered was not always stated. In two studies it was stated that the glycopeptides were administered intravenously<sup>13,22</sup> and in the other studies no mention was made about the administration of the antibiotics.

Two studies were based on prospective double-blind RCTs,<sup>13,22</sup> two studies included a

hypothetical cohort of patients using effectiveness data obtained from the published literature<sup>35,37</sup> and one economic evaluation was based on data from a single hospital where routine use of antibiotic prophylaxis changed from cephazolin to vancomycin and rifampicin.<sup>36</sup> Three studies undertook some form of decision analysis to synthesise data.<sup>13,35,37</sup> One model was informed by a single RCT<sup>13</sup> and the other models were informed by reviews of the literature. Little detail was provided about the sources searched or the designs of the studies from which data were obtained to inform the models. The sample size of patients varied from 119 patients in one arm of a trial in one study<sup>22</sup> to 599 in one arm of a trial in another study.<sup>36</sup> Two studies were based on decision analytic models and included a hypothetical cohort of patients.<sup>35,37</sup>

The length of patient follow-up varied considerably across studies. In one study, patients were followed up until they were discharged from hospital.<sup>13</sup> In another study, data relating to patients 3 months post-surgery were provided for the base case and up to 5 years for the reference case.<sup>37</sup> Marroni and colleagues included patients who were followed up for an average of 2 years.<sup>22</sup> For the remaining two studies, there was no information on the length of patient follow-up.<sup>35,36</sup>

None of the studies were conducted in the UK. The studies were conducted in Spain,<sup>13</sup> Italy,<sup>22</sup> Canada,<sup>35</sup> Australia<sup>36</sup> and the USA.<sup>37</sup> There may be resource implications in terms of transferring findings to the UK setting. With the exception of Zanetti and colleagues,<sup>37</sup> all studies were undertaken from the secondary care perspective. Costs were reported in Spanish pesetas,<sup>13</sup> US dollars<sup>22,35,37</sup> and Australian dollars.<sup>36</sup>

Codina and colleagues<sup>13</sup> undertook a cost-minimisation analysis comparing vancomycin with teicoplanin as antibiotic prophylaxis in elective cardiac surgery. Results were analysed by surgery type, either by CABG or VR. One group of patients were administered 1 g of vancomycin intravenously at induction of anaesthesia. They also received netilmicin 150 mg and a teicoplanin placebo. Patients undergoing VR received a second dose of vancomycin at the end of extracorporeal circulation. The other group of patients were administered 400 mg of teicoplanin intravenously at induction of anaesthesia. They also received netilmicin 150 mg and a vancomycin placebo. Patients undergoing VR received a second dose (200 mg of teicoplanin) at the end of extracorporeal circulation.

The analysis was based on a single-centre, double-blind, parallel-group RCT conducted in Spain and was undertaken from the secondary care perspective. There were 250 patients in each group, 233 undergoing VR surgery and 267 undergoing CABG. Patients were followed up until they were discharged from hospital.

The primary health outcomes that were measured included the rate of adverse drug reactions and the postoperative infection rates. No statistically significant differences were found in adverse drug reactions or postoperative infection rates for patients in the vancomycin group compared with the teicoplanin group. On this basis, the authors assumed that the health outcomes were equivalent across the interventions and therefore they based their evaluation on the difference in costs between the interventions.

Costs comprised the cost of the drug, the intravenous mix and the administration costs, together with personnel, capital and overhead costs, and this was consistent with the hospital perspective adopted by the study. Resource use was collected prospectively and was reported separately from costs, in appropriate physical units, helping to make the analysis transparent and potentially aiding study generalisability.

A decision tree was used to evaluate two scenarios: antibiotic administration in (1) the surgical room theatre and (2) the medical ward. For the CABG patients, when the antibiotics were administered in the surgical room, the cost was 12,005 pesetas (pts) per patient (1998 prices) for those who received vancomycin and 8265 pts for those who received teicoplanin. In contrast, when the antibiotics were administered in the medical room, the cost was 2809 pts for those who received vancomycin and 6740 pts for those who received teicoplanin. For the valve replacement patients, when the antibiotics were administered in the surgical room, the cost was 14,528 pts for those who received vancomycin and 11,661 pts for those who received teicoplanin. If the antibiotics were administered in the medical ward, the cost was 10,140 pts for those who received vancomycin and 5308 pts for teicoplanin.

The authors concluded that the cost of antibiotic prophylaxis among cardiac surgery patients depends heavily on the setting and the circumstances of the drug administration. Based on the cost-minimisation analysis, vancomycin was the least costly option when administered within the medical ward, whereas teicoplanin was the

most cost-effective option if the drug was administered within the surgical area. The authors note that if vancomycin is used in the medical ward, it is important that the right plasmatic drug levels of the antibiotic are administered at the beginning of the surgical procedure.

The authors justified their decision to undertake a cost-minimisation analysis due to the number of adverse drug events being equivalent across the treatments. The analysis can be considered as a partial economic evaluation analysis, since the authors did not make full use of all the available outcomes data, some of which did show across comparator differences. Costs were treated deterministically; however, patient-level data did allow for stochastic analysis in which it would have been possible to quantify the uncertainty associated with the cost-effectiveness estimates. No data were reported on MRSA. The impact of antibiotic resistance on long-term effectiveness of antibiotic prophylaxis was not considered within the analysis.

Marroni and colleagues<sup>22</sup> undertook a cost-minimisation analysis comparing teicoplanin with cefazolin as antibiotic prophylaxis in prosthetic vascular surgery. Adults undergoing elective abdominal aortic and lower-extremity peripheral vascular surgery were included in the study. A single intravenous 400-mg dose of teicoplanin was compared with a 2-g dose of cefazolin at the induction of anaesthesia. The analysis was based on a single-centre, double-blind RCT conducted in Italy and was undertaken from the secondary care perspective. There were 119 patients in each group and the aim was to follow up patients for 1 year post-hospital discharge. In practice, the mean length of follow-up was 24 months.

The primary health outcomes that were measured included the rate of prosthetic and wound infections. Postoperative infections were defined using the CDC criteria. Secondary health outcomes included mortality and side-effects. Antibiotic-related nephrotoxicity was considered but ototoxicity was not considered.

In total, SSIs were reported for seven (5.9%) patients in the teicoplanin group, two (1.7%) of which were in grafts and five (4.2%) of which were in wounds, and two (1.7%) patients in the cefazolin group. One patient in the teicoplanin group developed an anastomotic aneurysm and MSSA was isolated from the aneurysm: the patient was cured and had no sign of infection 24 months later.

Early superficial wound infections, diagnosed a mean of 9 days after surgery, were reported in five (4.2%) patients in the teicoplanin group and two (1.7%) in the cefazolin group. Of the five infections in the teicoplanin group, two were microbiologically tested as CNS plus *Proteus mirabilis* and *Enterobacter cloacae*. Of the two infections in the cefazolin group, one was identified as MSSA plus *Proteus mirabilis*.

Other postoperative infections reported in patients' postoperative stay included 12 in the teicoplanin group, of which eight (7%) patients had pneumonia and four (3%) had urinary tract infections, and 14 patients in the cefazolin group, with eight (7%) pneumonia infections, three (2.5%) urinary tract infections and three (2.5%) bloodstream infections.

Four (3.4%) deaths were reported in the teicoplanin group and three (2.5%) in the cefazolin group. One death in each group was related to infection.

No side-effects were reported that related to antibiotic prophylaxis.

The costs that were measured included the cost of the antibiotics and the daily cost of the hospital stay. The total cost of care for the teicoplanin group was US\$571,572 and for the cefazolin group it was US\$519,062, giving a difference in costs of US\$52,510 (price year not stated). Cost savings using cefazolin were related to the lower cost of the drug and the shorter duration of the hospital stay.

The authors justified their decision not to compare costs with effects because there were no statistically significant differences in effects measured between the two groups. Sensitivity analysis was not undertaken. The analysis was deterministic. Unit cost information was not provided and this undermines the transparency of the results. The source of the price/cost data is not clear. No data were reported on MRSA. The impact of antibiotic resistance on long-term effectiveness of antibiotic prophylaxis was not considered.

Phillips and colleagues<sup>35</sup> undertook a cost-effectiveness analysis comparing six strategies for antimicrobial prophylaxis in cardiovascular surgery patients who were labelled penicillin allergic. The six strategies were:

1. Vancomycin given to all patients labelled penicillin allergic.

2. Cefazolin given to all patients labelled penicillin allergic.
3. Obtain a history from all patients who were labelled penicillin allergic and then give (a) vancomycin to all patients with a history suggesting an immunoglobulin E (IgE)-mediated reaction to penicillin and (b) cefazolin to patients without a history of IgE-mediated reaction.
4. Administer penicillin tests to patients with a history suggesting an IgE-mediated reaction to penicillin, give vancomycin to patients with a positive skin test and cefazolin to all others.
5. Administer penicillin tests to all patients labelled penicillin allergic and then give vancomycin to patients with a positive skin test and cefazolin to all patients with a negative skin test, regardless of history.
6. Administer penicillin tests to patients with all patients labelled penicillin allergic and then give vancomycin to patients with either a positive skin test or a history suggesting an IgE-mediated reaction to penicillin and give cefazolin to all others.

The analysis was based on a decision tree, informed by data in the published literature. The analysis was undertaken in Canada, from the secondary care perspective. The study population comprised a hypothetical cohort of cardiovascular surgery patients who were labelled penicillin allergic. It is not clear whether the surgery was elective. The length of follow-up was not stated but this was likely to be the length of the postoperative stay in hospital.

Two primary health outcomes were measured, that is, the rate of serious non-life-threatening reactions and the rate of potentially life-threatening anaphylactic episodes. The rate of serious non-life threatening reactions was 0.03 with strategies (1), (2) and (3), 0.02 with strategy (4) and 0.0175 with strategies (5) and (6). The rate of potentially life-threatening anaphylactic episodes was 0.0004 with strategy (1), 0.0003 with strategy (2), 0.0002 with strategy (3), 0.00027 with strategy (4), 0.00021 with strategy (5) and 0.000134 with strategy (6).

Costs included the cost of the antibiotics, the penicillin and cephalosporin skin tests and the treatment of serious adverse reaction to vancomycin and cefazolin. The authors did not provide details on resource use. Data on unit costs were reported; however, the price year was not provided.

An incremental cost-effectiveness analysis was calculated to combine the costs and benefits of the

six strategies, relative to strategy (2). Based on the rate of serious non-life-threatening reactions, strategy (2) dominated strategies (1) and (3). The incremental cost per serious non-life-threatening reaction avoided with strategy (4) was US\$5426 (price year not stated). For strategy (5), the incremental cost-effectiveness ratio (ICER) was US\$10,024 and with strategy (6) it was US\$10,906. Based on the rate of potentially life-threatening anaphylactic shock, the incremental cost per reaction avoided was US\$166,667 with strategy (3), US\$159,204 with strategy (1), US\$428,571 with strategy (4), US\$692,308 with strategy (5) and US\$544,776 with strategy (6) when compared with strategy (2). The authors concluded that selective use of vancomycin is more cost-effective than indiscriminate use of vancomycin in cardiovascular surgery patients who are labelled penicillin allergic.

Univariate sensitivity analyses were conducted to address the issue of uncertainty in the parameter estimates included in the model. All estimates were varied and, for the probability values, ranges were taken from the published literature. No justification was provided for the variation in costs. The results of the sensitivity analyses suggested that the rate of serious non-life threatening reactions had the most important impact on the ICER. It was found that unrealistic changes had to be made to parameter estimates for strategy (1) to become the most cost-effective strategy.

It is not clear how the authors obtained the estimates to include in their model or how they combined any data that they did obtain from the literature. The analysis was deterministic. No data were reported on MRSA. The impact of antibiotic resistance on long-term effectiveness of antibiotic prophylaxis was not considered.

Spelman and colleagues<sup>36</sup> undertook a cost-consequence analysis, comparing cefazolin with vancomycin and rifampacin in antibiotic prophylaxis for cardiac surgery. It is not clear whether the surgery was elective. Intravenous cefazolin was administered in four 1-g doses, that is, 1 g preoperatively and 3 g postoperatively. A 1-g amount of intravenous vancomycin was administered and 600 mg of oral rifampacin preoperatively, with a second dose of vancomycin 12 hours postoperatively. Patients were given oral rifampacin in the ward before being transferred to the operating room where, on arrival, they were given the vancomycin. The vancomycin was infused over about 1 hour. There were 599

patients in the cefazolin group and 515 patients in the vancomycin and rifampicin group.

The data were obtained from a single hospital before and after a change in the routine use of antibiotic prophylaxis in surgery from cefazolin to vancomycin and rifampicin. The analysis was undertaken in Australia, from the secondary care perspective. The study population comprised those undergoing CABG. The length of follow-up per patient was not stated; the total length of data collection was 12 months for each type of drug regimen.

The health outcomes measured were the rate of deep sternal wound infection and the overall rate of infections. Following the switch from cefazolin, the number of deep infections fell from 28 (4.7 infections per 100 procedures, 95% CI 3.1 to 6.7), of which 25 were deep sternal infections (4.2 per 100 procedures) to three infections (0.6 per 100 procedures, 95% CI 0.1 to 1.7;  $p < 0.001$ ). For deep sternal wound infection, the absolute risk reduction was 0.36, the RR reduction was 86% and the number of patients needed to treat to prevent one infection was 28.

Following the switch from cefazolin, the number of infections fell from 63 (10.5 infections per 100 procedures) to 25 (4.9 infections per 100 procedures) (95% CI 3.2 to 7.1;  $p < 0.001$ ). The absolute risk reduction following use of vancomycin and rifampicin was 0.056, the RR reduction was 55.3% and the number of patients needed to treat to prevent one infection with the new regimen was 18.

There was a reduction in the bacteriology of SSI over the course of the study with MRSA accounting for 67% of infections when cefazolin was used and not being present when using vancomycin and rifampicin. MSSA was detected in five infected patients in the cefazolin group and in two infected patients in the vancomycin and rifampicin group. Ten skin or enteric flora were reported in each of the infected groups. There was no growth/specimen in three infected patients in the cefazolin group and four infected patients in the vancomycin and rifampicin group. There were three Enterobacteriaceae infections in the cefazolin group and seven in the vancomycin and rifampicin group. Additionally, there were two other infections in the vancomycin and rifampicin group. It should be noted that no regular VRE screening was performed but there were three cases of VRE bacteraemia in each 12-month period.

Costs were based on resources used in hospital and were taken from a different patient sample compared with that used in the effectiveness study. Limited details of the cost analysis were presented. The mean length of postoperative stay related to cefazolin was 9.9 days compared with 10.2 days in the vancomycin and rifampicin group. The additional cost per deep sternal wound infection was A\$31,597 (no price date). The excess total cost of infections was A\$789,925 for the cefazolin group. The gross cost savings by using vancomycin and rifampicin were A\$600,343 and the cost of this was A\$23,688, giving a net saving from using this strategy of A\$576,655.

Costs and benefits were not combined. The authors concluded that cost savings were obtained and there was a statistically significant decrease in the total rates of SSI and deep SSI when using vancomycin and rifampicin compared with cefazolin, which suggests that this is the dominant strategy. The study did not consider the impact of antibiotic resistance on the long-term effectiveness of antibiotic prophylaxis.

Zanetti and colleagues<sup>37</sup> undertook a cost-effectiveness analysis and a cost-utility analysis based on a decision analytic approach, informed by data in the published literature. A state-transition model was used for the reference case analysis to incorporate the lifetime probability of death, myocardial infarction, angina or asymptomatic coronary artery disease following CABG to estimate life expectancy, quality-adjusted life expectancy and total lifetime costs.

The use of five doses of 1 g of vancomycin administered over 48 hours for perioperative prophylaxis against SSI in patients undergoing CABG was compared with six doses of cefazolin over 48 hours. The analysis was undertaken in the USA and the base case analysis was reportedly undertaken from the societal perspective, although there was no inclusion of productivity losses. The reference case was undertaken from the healthcare payer perspective. The study population for the base case analysis comprised a hypothetical cohort of 10,000 patients who underwent CABG. The reference case analysis was based on a 65-year-old man with stable, multi-vessel coronary heart disease. It was not clear whether surgery was elective. The length of follow-up was 3 months post-surgery for the base case and 5 years for the reference case.

The base case analysis measured outcomes using the number of deep SSIs avoided, the number of

superficial SSIs avoided and the number of hospital deaths averted. The reference case analysis used quality-adjusted life-years (QALYs). Additionally the following outcomes were measured: incidence of causative organisms, the RR of SSI caused by susceptible organisms, the incidence of antibiotic-related AEs, the incidence of SSI due to resistant organisms and the probability of hospital death.

The authors provide a table which reports on the model variables; however, some of the data are difficult to interpret since it is not clear whether they are probabilities or rates. The incidence of superficial SSI was 0.08 (plausible range 0.02–0.12). The incidence of deep SSI was 0.04 (plausible range 0.01–0.06). The RR of SSI caused by susceptible organisms was estimated to be the same for vancomycin versus no prophylaxis and cefazolin versus no prophylaxis at 0.4 (plausible range 0.2–0.8). It is not clear if these figures refer to a rate.

The organisms causing SSI were *S. aureus* 0.25 (plausible range 0.2–0.35), CNS 0.25 (plausible range 0.2–0.35), enterococci 0.05 (plausible range 0.02–0.15) and Gram-negative bacteria 0.3 (plausible range 0.15–0.5). It seems that these data are probabilities, but it is not clear.

The incidence of SSI due to resistant organisms was 0.012 (plausible range 0–0.03) for MRSA (as a proportion of all SSIs due to *S. aureus*), 0.024 (plausible range 0–0.03) for MR-CNS (as a proportion of all SSIs due to CNS), 0.003 (plausible range 0–0.006) for VRE (as a proportion of all SSIs due to enterococci) and 0.01 (plausible range 0–0.036) for cefazolin-susceptible Gram-negative bacteria (as a percentage of all SSIs due to Gram-negative bacteria). A history of allergy to  $\beta$ -lactams was estimated at 0.1 (plausible range 0.05–0.15). The incidence of vancomycin-related AEs was 0.08 (plausible range 0.01–0.2) and the incidence of cefazolin-related AEs was 0.08 (plausible range 0.01–0.2). The probability of hospital death due to deep SSI was 0.082 (plausible range 0.01–0.1), due to an antibiotic allergic reaction 0.00002 (no range provided) and due to CABG surgery-related events 0.036 (plausible range 0.01–0.1).

For the reference case, QALYs were estimated by applying weights to the health states representing death, myocardial infarction, angina or asymptomatic coronary artery disease. Quality weights were obtained from the Beaver Dam Health Outcomes Study, in which the time trade-

off technique was used to elicit utilities.<sup>38</sup> It was not stated who provided these valuations. A wide range of quality weights for temporary health states were explored for superficial and deep SSI.

For the base case, it was found that if no antibiotic prophylaxis was given, 570 patients would develop a deep SSI and for every 10,000 patients there would be 405 hospital deaths. Routine use of vancomycin would result in 368 deep SSIs and 388 hospital deaths per 10,000 patients. Routine use of cefazolin would result in 397 deep SSIs and 391 hospital deaths per 10,000 patients.

For the reference case, use of routine vancomycin would result in a gain of 8.339 QALYs for the 65-year-old male, compared with 8.335 QALYs for use of cefazolin. The incremental QALY for cefazolin versus no prophylaxis was 0.023 and the incremental QALY for vancomycin versus cefazolin was 0.004.

Costs included the use of the antibiotics and perfusion, SSI, hospital deaths, medical charges and AEs and were obtained from the published literature. Unit costs were not reported and neither was resource use. Future costs (and benefits) were discounted at an annual rate of 3%.

For the base case, if no antibiotic prophylaxis was used, the total cost per 10,000 patients was US\$33,410,000 (1998 price year). US\$23,360,000 of vancomycin was administered and US\$24,530,000 if cefazolin was administered. It was calculated that an incremental saving of US\$8,880,000 per 10,000 patients would be gained from using cefazolin instead of no antibiotic prophylaxis and US\$1,170,000 per 10,000 patients from using vancomycin rather than cefazolin.

For the reference case, the lifetime cost was US\$62,892 if no antibiotic prophylaxis was administered and US\$61,913 when administering vancomycin and US\$62,016 using cefazolin prior to surgery. The use of cefazolin rather than no antibiotic prophylaxis resulted in an incremental saving of US\$876. The use of vancomycin rather than cefazolin resulted in an incremental saving of US\$103.

Costs and benefits were not synthesised. The cefazolin strategy dominated the no prophylaxis strategy. The vancomycin strategy was as cost saving and as effective as the cefazolin strategy. The authors suggested that there may be a trade-off between short-term benefits to individual

patients and long-term consequences for society in terms of increased antibiotic resistance. Due to a lack of data on the societal consequences that might result, the authors were reluctant to recommend a change in practice.

Univariate and multivariate sensitivity analysis was undertaken to explore the impact of variability on the estimates used in the model. Sensitivity analysis was conducted on the plausible ranges that were used as parameters for the analysis. Additionally, the potential variation in the cost of the antibiotics and the cost of administering them, and the use of different SSI rates, were explored in sensitivity analyses. The sensitivity analyses showed that no prophylaxis was always the most costly and the least effective option. The ranking of vancomycin compared with cefazolin was not affected by the sensitivity analyses. Results were most sensitive to changes in the cost of vancomycin, its efficacy and that of cefazolin, and the prevalence of bacterial resistance to antibiotics.

The authors did not model the relationship between antibiotic prophylaxis and resistance, due to lack of data. However, they did conduct sensitivity analyses to explore the impact of a decrease in efficacy of vancomycin on study results. They argued that the routine use of vancomycin would remain more effective and less costly than the routine use of cefazolin if all enterococci were resistant to vancomycin because of the small proportion of SSIs caused by enterococci postoperatively. They simulated a hypothetical scenario in which prevalence of VRE would continue to increase by 2% per year, as reported in US hospitals from 1989 to 1997, and assumed the same trend for staphylococci. They assumed that vancomycin prophylaxis, but not cefazolin prophylaxis, would accelerate this trend by 50%. The result was that after 6 years vancomycin was no longer less costly than routine cefazolin and would become less effective over 13 years. However, this result was based on author assumption about resistance rates and they argued that no conclusions could be drawn from it.

## Discussion

Four out of five of the studies focused on condition-specific measures of effect such as the rate of postoperative prosthetic and wound infections and AEs including mortality and side-effects.<sup>13,22,35,36</sup> Zanetti and colleagues included a generic measure of preference-based health-related quality of life, based on time trade-off valuations.<sup>37</sup> For the reference case, QALYs were calculated, as favoured by NICE (<http://www.nice.org.uk/>).<sup>39</sup>

Three studies calculated ICERs and undertook sensitivity analyses,<sup>13,35,37</sup> only one of which included multivariate sensitivity analysis.<sup>37</sup> No studies undertook probabilistic sensitivity analysis.

Only one of the studies explored the implications of antibiotic resistance in any detail,<sup>37</sup> although two of the other studies noted the bacteriological organisms found in existing SSI.<sup>22,36</sup> Zanetti and colleagues undertook an exploratory sensitivity analysis to assess the impact of resistance in terms of a reduction in the efficacy of vancomycin on the study results.<sup>37</sup>

## Summary

The conclusions from this review are as follows:

- Only one study incorporated health-related quality of life and undertook a cost–utility analysis, the approach favoured by NICE.
- SSI can increase patient length of stay considerably, which has substantial cost implications. The length of hospital stay is the key cost driver from the secondary care perspective.
- None of the studies was undertaken in the UK, limiting the transferability of the results to the UK setting.
- No studies explicitly modelled antibiotic resistance as part of the primary analysis.





## Chapter 5

# Supplementary economic reviews

### Introduction

This chapter provides details of a series of literature reviews relating to issues of cost-effectiveness in the context of the management of MRSA. In addition to conducting a systematic review of the effectiveness evidence on glycopeptide antibiotics compared with non-glycopeptide antibiotics, the research brief was to conduct a review of the corresponding cost-effectiveness evidence to inform the development of an economic model. A key objective was to assess the impact of antibiotic prophylaxis on MRSA infection rates in surgical patients and to explore the potential longer term consequences the use of these antibiotics may have in terms of increased antibiotic resistance. To address this, four supplementary reviews were undertaken to broaden the scope of the review and to expand the potential pool of data that were available for use in developing the economic model. Details of the literature searches for these supplementary reviews are provided in Appendix 1.

The first supplementary review assessed the published economic evaluation literature which compared the costs and effects associated with the use of any antibiotic prophylaxis for surgery, excluding glycopeptides. The purpose of this review was to characterise the methods used in economic evaluations of antibiotic prophylaxis for surgery, including interventions other than glycopeptides. This review could provide useful information about how to conduct evaluations in this field and it provided the opportunity to use indirect evidence to strengthen the inference concerning the relative efficacy of the treatments for comparison. The cost-effectiveness review in Chapter 4 assessed studies that made direct comparisons with glycopeptides – that is, it included evaluations of glycopeptides compared with other antibiotics (e.g. interventions A versus B and B versus C, where B was a glycopeptide and A and C were non-glycopeptides). This review included studies that could be used as **indirect** evidence (e.g. studies comparing interventions A with C).

A second supplementary cost-effectiveness review was undertaken to assess economic evaluations of

antibiotics where antibiotic resistance is a problem and, therefore, looked beyond antibiotic prophylaxis used in surgery. The purpose of this review was to explore the methodological approaches used to evaluate the antibiotic resistance problem.

A further two selective reviews were undertaken to enhance the development of an economic model. The first of these explored the literature on the use of epidemiological and decision analytic models in infectious diseases where resistance to antibiotics is an issue. The purpose was to obtain examples of methodological approaches to assessing and modelling the impact of antibiotic resistance in cost-effectiveness analyses. The final review explored the published literature to develop a conceptual evaluative framework for the economic evaluation of policies against MRSA. It considers different dimensions of the evaluation problem and a number of methodological approaches which might be applied to deal with these problems.

### Economic evaluations of non-glycopeptide antibiotic prophylaxis for surgery

#### Methods

##### *Inclusion criteria*

Studies that were full economic evaluations were considered: (1) cost-effectiveness evaluations, including cost-minimisation and cost-consequence analyses; (2) cost-utility analyses; and (3) cost-benefit analyses.<sup>34</sup> Comparator interventions had to include non-glycopeptide antibiotic prophylaxis for surgery.

##### *Data extraction and quality assessment*

Data were extracted on key components of standard economic evaluations including data on the comparators, study population, the length of prophylaxis, the type of surgery, the setting and perspective, the costs and outcomes measured, the definition of infection used, details of adverse drug reactions, the length of follow-up, estimates of incremental cost-effectiveness, how antibiotic resistance was handled, the risk of confounding,

costs attributable to infection and details of sensitivity analyses.

## Results

Key methodological issues in this area, apart from general economic evaluation method quality criteria, are the use of appropriate comparators, study population, the length of prophylaxis, the type of surgery, the costs and outcomes measured, the definition of infection used, details of adverse drug reactions, the length of follow-up, how antibiotic resistance was handled, the risk of confounding and methods used to determine costs attributable to infection. The studies were examined for any helpful lessons learnt that could be applied to the economic evaluation of glycopeptides, in addition to the economic evaluations of glycopeptides reviewed in Chapter 4.

Forty-three studies were obtained from the searches. Of these, 23 economic evaluations of antibiotic prophylaxis were reviewed. However, one economic evaluation was excluded because it was in Japanese and there was no English version of the abstract.<sup>40</sup>

Of the remaining 22 economic evaluations, 12 were RCTs. Eight were based on non-randomised cohorts and two were secondary economic evaluations, using meta-analyses.

The surgical groups were cardiothoracic (3), ear, nose and throat (ENT) (1), orthopaedic (2), abdominal and gynaecological (5), vascular (1), urological (2), head and neck (2), maxillofacial (1), penile prosthesis implants (1), breast (1), multiple surgical groups (1), inguinal hernia repair (1) and

appendectomy (1). Only four trials had fewer than 100 patients.

Oral, intravenous and topical antibiotics were evaluated, but most studies examined the use of intravenous antibiotics only. *Table 10* provides details of the prophylaxis regimens assessed by the evaluations and *Table 11* provides full details of all the included studies.

The length of prophylaxis was not always stated, but ranged from one dose preoperatively, to 7-day courses of antibiotics. Adverse drug reactions (ADRs) were not usually reported, and when they were reported there was a wide variation. ADR rates reported by Paladino and colleagues comparing ampicillin–sulbactam with cefoxitin were around 20%.<sup>58</sup> Other studies reported much lower rates.

## Discussion

The main outcomes used were condition specific: wound and SSIs, although variable definitions were applied. Diagnosis was usually based on clinical criteria, although some also included microbiological culture. Some studies appeared to differentiate between joint, deep and superficial/incisional wound infections. No generic measures of quality of life (QoL) or morbidity data were reported other than impact on length of hospital stay.

Costs were poorly reported in most studies. Two studies did not report actual costs at all<sup>41,45</sup> and seven only reported costs for the antibiotics.<sup>46,53,55,58–60,62</sup> The remaining studies combined the cost of the antibiotics with locally determined or national tariff charges for increased

**TABLE 10** Types of antibiotic prophylaxis compared in the economic evaluations

Study	Combinations	Number of studies
Pearson, 1996; <sup>41</sup> Blair, 1995; <sup>42</sup> VandenBergh, 1996; <sup>43</sup> Pearle, 1997; <sup>44</sup> Schilling, 1997; <sup>45</sup> Wieck, 1997; <sup>46</sup> Bold, 1998; <sup>47</sup> Kapoor, 1998; <sup>48</sup> Kulling, 2000; <sup>49</sup> Lazorthes, 1992 <sup>50</sup>	Active versus placebo	10
Albers, 1994 <sup>51</sup>	One or more of the comparators not stated	3
Davey, 1995; <sup>52</sup> Pestotnik, 1996; <sup>53</sup> Schwartz, 1996; <sup>54</sup> Pavan, 1992 <sup>55</sup>	One or more of the comparators a combination of more than one prophylaxis regimen	4
Thomas, 1999; <sup>56</sup> Rau, 2000 <sup>57</sup>	Comparison of two cephalosporins	2
Paladino, 1994; <sup>58</sup> Heit, 1997; <sup>59</sup> Hall, 1993; <sup>60</sup> Roach, 1990; <sup>61</sup> Rau, 2000 <sup>57</sup>	Cephalosporin versus a penicillin	5
Fried, 1996 <sup>62</sup>	Culture specific	1

TABLE 11 Summary of the economic evaluations identified in the review of non-glycopeptide antibiotics prophylaxis for surgery

Author, year, country of origin, study design	Alternatives under investigation (n)	Surgery and patient group	Methods used (primary or secondary economic analysis)	Results	Comments
Roach, 1990, <sup>61</sup> USA, CCT	Comparators: Cefazolin, cefazolin plus gentamicin, cefamandole, cefamandole plus gentamicin Length of prophylaxis: All administered i.v. at induction. The cephalosporins were administered intraoperatively and continued 72 hours postoperatively. Gentamicin was administered as a single preoperative dose	Surgery: Cardiothoracic surgery, elective median sternotomy Patient group: Adults	1 <sup>Y</sup> or 2 <sup>Y</sup> : 1 <sup>Y</sup> Perspective: Secondary care Costs: Costs of antibiotic administration (including drugs and hospital charges) and management of wound infections that occurred in spite of prophylaxis Outcomes: Infections Definition of infection: Not reported ADRs: Not reported Length of follow-up: Unclear	Difference in effect: The only significant difference was the low rate of sternal wound infections among cefamandole/gentamicin patients vs cefazolin/gentamicin patients (0 vs 2.4% respectively; $p < 0.02$ ). Comparing outcomes for all patients receiving cefamandole ( $n = 522$ ) vs cefazolin ( $n = 508$ ), infection rates at sternal sites were 0.4% vs 1.8%, respectively ( $p < 0.05$ ) and donor sites were 0% vs 1.3% ( $p < 0.02$ ). Difference in cost: Prophylaxis and wound management costs were US\$766 per patient for the cefazolin group and US\$315 for the cefamandole group ICER: None	Handling of resistance: No Risk of confounding: Medium Costs attributable to infection: Cost of administration and wound management infections Sensitivity analysis: No Other comments: Study design unclear. Limited cost analysis
Lazorthes, 1992, <sup>50</sup> France, RCT	Comparators: Single-dose 750 mg of cefamandole administered directly to the operative wound with local anaesthesia [added to xylocaine (lidocaine solution)] ( $n = 162$ operations, $n = 155$ patients) vs no antibiotics ( $n = 162$ operations, $n = 153$ patients) Length of prophylaxis: Single dose	Surgery: Inguinal hernia repair Patient group: Adults and children	1 <sup>Y</sup> or 2 <sup>Y</sup> : 1 <sup>Y</sup> Perspective: Secondary care and care at home Costs: Drug costs, medical home care, Outcomes: Wound abscesses, microbiological investigations Definition of infection: Not stated ADRs: None reported Length of follow-up: Up to 1 month postoperatively	Difference in effect: 7 wound abscesses occurred, all in the no antibiotics group ( $p = 0.007$ ) Difference in cost: The total cost of cefamandole was US\$517 (no price date). The total cost of home care (based on nurse salaries) was US\$1564 for the no antibiotics group. The hospital length of stay was prolonged in 4/7 cases in the antibiotics group but this was not costed ICER: None	Handling of resistance: No Risk of confounding: Low Costs attributable to infection: Home care costs Sensitivity analysis: Not conducted Other comments: Very limited cost analysis

continued

TABLE 11 Summary of the economic evaluations identified in the review of non-glycopeptide antibiotics prophylaxis for surgery (cont'd)

Author, year, country of origin, study design	Alternatives under investigation (n)	Surgery and patient group	Methods used (primary or secondary economic analysis)	Results	Comments
Pavan, 1992, <sup>55</sup> Canada. Phase 1: retrospective chart review, randomly selected. Phase 2: prospective chart review	Comparators: Phase 1: no antibiotics, cefoxitin 1 g or 2 g single dose, more than one dose of cefoxitin, other antibiotics, n = 43 Phase 2: combination of cefazolin plus metronidazole vs cefotetan (for cefoxitin), no antibiotics other, n = 52 Length of prophylaxis: 79% of patients received antibiotics postoperatively	Surgery: Uncomplicated appendectomies Patient group: Adults and children	I <sup>IV</sup> or 2 <sup>IV</sup> : I <sup>IV</sup> Perspective: Secondary care Costs: Antibiotic therapy not including i.v. mixing equipment or nursing administration costs Outcomes: Infection rates Definition of infection: Either discharge or pus whether pathogenic organisms were isolated or not, or the discharge of serous fluid from which pathogenic organisms were isolated ADRs: None reported Length of follow-up: Up to 3 weeks post hospital discharge	Difference in effect: Not reported by drug. Comparing phase 1 with phase 2, no evidence of any ADRs. In phase 1, 7% of patients had a wound infection postoperatively, whereas in phase 2, one patient showed signs of an early infection Difference in cost: Phase 1: average cost per person of cefoxitin was Can\$77.00 (no price year) vs average cost per person of antibiotics was Can\$13.55 ICER: None	Handling of resistance: No Risk of confounding: Medium to high Costs attributable to infection: Unclear Sensitivity analysis: Other comments: Limited cost analysis
Hall, 1993, <sup>60</sup> Australia, RCT using non-stratified, blocked randomisation with cell sizes of 10	Comparators: Ceftriaxone 1 g single dose (n = 515) vs a 48-hour regimen consisting of flucloxacillin plus gentamicin (n = 516) Length of prophylaxis: Ceftriaxone 1 g vs flucloxacillin 2 g after induction, 1 g at commencement of cardiac bypass and thereafter 18 every 4 hours for 48 hours plus gentamicin 1.3 mg/kg after induction and thereafter 1.3 mg/kg body weight every 8 hours for 48 hours. Dose adjustments made	Surgery: Cardiac surgery Patient group: Adults and children	I <sup>IV</sup> or 2 <sup>IV</sup> : I <sup>IV</sup> Perspective: Secondary care Costs: Acquisition and administration of drugs Outcomes: Surgical site infection, ASEPSIS score, other nosocomial events (e.g. febrile period, death), microbiological investigations Definition of infection: A major wound infection was a purulent wound discharge or a serous wound discharge with culture of pathogenic organisms. Serous wound discharges with negative culture results and also stitch abscesses were classified as minor wound infections ADRs: ADRs reported	Difference in effect: Major wound infection (sternum) ceftriaxone 14/515: flucloxacillin and gentamicin 8/516 (p = 0.20). Major wound infection (limbs) ceftriaxone 16/377: flucloxacillin and gentamicin 21/386 (p = 0.44). Minor wound infection (sternum) ceftriaxone 37/515: flucloxacillin and gentamicin 41/516 (p = 0.65). Minor wound infection (limbs) ceftriaxone 42/377: flucloxacillin and gentamicin 47/386 (p = 0.66). Culture isolates were available, as were ASEPSIS scores. Length of stay in ICU or in hospital not	Handling of resistance: Not reported, no MRSA isolated Risk of confounding: Low Costs attributable to infection: Not reported Sensitivity analysis: Not undertaken Other comments: Cost analysis limited

continued

TABLE 11 Summary of the economic evaluations identified in the review of non-glycopeptide antibiotics prophylaxis for surgery (cont'd)

Author, year, country of origin, study design	Alternatives under investigation (n)	Surgery and patient group	Methods used (primary or secondary economic analysis)	Results	Comments
Albers, 1994, <sup>51</sup> The Netherlands, matched control	Comparators: Surgical patients versus non-infected surgical patients (antibiotic prophylaxis not clear) intervention = 16 (8 superficial infections, 8 deep infections), matched control = 16 similar non-infected patients Length of prophylaxis: Not stated	Surgery: Closed fractures Patient group: Adult mixed surgical and trauma	Length of follow-up: 6 weeks after operation or, if hospital stay prolonged, until time of hospital discharge  1 <sup>Y</sup> or 2 <sup>Y</sup> : 1 <sup>Y</sup> Perspective: Secondary care Costs: Standard cost per bed day plus antibiotics Outcomes: Not reported Definition of infection: Clinical: superficial and deep ADRs: Not reported Length of follow-up: Hospital stay	statistically significantly different across groups Difference in cost: Ceftriaxone therapy costs were 22% of those of the flucloxacillin/gentamicin group (A\$17,248 vs A\$78,510) (price year not reported) ICER: None reported  Difference in effect: Not reported Difference in cost: Patients with superficial wound infections did not cost more than non-infected controls, deep infection cost DFI35,224 more than non-infected controls ICER: None	Handling of resistance: Not reported Risk of confounding: High Costs attributable to infection: Identified by comparing infected with non-infected patients. Patients with superficial wound infections did not cost more than non-infected controls, deep infection cost DFI35,224 more than non-infected controls Sensitivity analysis: None Other comments: No specific antibiotic prophylaxis reported
Paladino, 1994, <sup>58</sup> USA, RCT	Comparators: Ampicillin-sulbactam 3 g (n = 68) vs cefoxitin 2 g (n = 68). Oral neomycin and erythromycin given to 49/61 colorectal patients Length of prophylaxis: 30 minutes before incision, 6 h later, 3rd dose 6 h later for colorectal surgery	Surgery: Colorectal, upper GI/biliary, other abdominal, "clean/contaminated" Patient group: Adults at risk of developing SSI	1 <sup>Y</sup> or 2 <sup>Y</sup> : 1 <sup>Y</sup> Perspective: Hospital Costs: Drug costs only Outcomes: Overall infection, wound infection, ADRs Definition of infection: Clinical and microbiological ADRs: Ampicillin-sulbactam 13.2%, cefoxitin 19.1% (included PONV) Length of follow-up: Hospital stay	Difference in effect: postoperative infection rate: ampicillin-sulbactam 12.9%, cefoxitin 9.8%, wound infection rate 1.6% in both groups. Outcomes the same Difference in cost: The difference in cost was based on the acquisition price. The 1993 direct price of cefoxitin 2 g was \$13.59 versus ampicillin-sulbactam 3 g at \$9.80 ICER: CMA	Handling of resistance: Not mentioned Risk of confounding: Method of randomisation not reported Costs attributable to infection: Not reported Sensitivity analysis: Not reported Other comments: Gram-positive and Gram-negative infections. Incomplete costs

continued

TABLE 11 Summary of the economic evaluations identified in the review of non-glycopeptide antibiotics prophylaxis for surgery (cont'd)

Author, year, country of origin, study design	Alternatives under investigation (n)	Surgery and patient group	Methods used (primary or secondary economic analysis)	Results	Comments
Blair, 1995, <sup>42</sup> USA, retrospective cohort	Comparators: Use of prophylactic antibiotics (n = 93) vs none (n = 99) Length of prophylaxis: Started preoperatively and continued for 24 h or longer	Surgery: Clean neck dissection Patient group: Adults	I <sup>Y</sup> or 2 <sup>Y</sup> : 1 <sup>Y</sup> Perspective: Secondary care Costs: Individual patient charges Outcomes: Wound infection Definition of infection: Used a published wound grading scale ADRs: Not reported Length of follow-up: Hospital stay	Difference in effect: No difference in wound infection rates Difference in cost: US\$36,030 additional cost for an infected patient ICER: Not reported	Handling of resistance: None Risk of confounding: High Costs attributable to infection: Extra costs caused by longer hospital stay minus costs of antibiotics Sensitivity analysis: None reported Other comments: Authors stated that study not large enough to detect a difference, range of antibiotics used
Davey, 1995, <sup>52</sup> UK, meta-analysis and modelling	Comparators: Amoxicillin/clavulanic acid (ACA) vs multiple alternatives Length of prophylaxis: not stated	Surgery: Elective abdominal Gynaecological Combined Patient group: Colorectal: 4 trials Combined: 6 trials Gynaecological: 3 trials	I <sup>Y</sup> or 2 <sup>Y</sup> : 2 <sup>Y</sup> Pooled effectiveness data for multiple alternatives to ACA Perspective: Secondary care Costs: Antibiotics and "cost per wound infection" from UK published data Outcomes: Wound infection rates Definition of infection: Not reported ADRs: Not reported Length of follow-up: Hospital stay	Difference in effect: See ICER Difference in cost: Many reported ICER: Cost per wound infection prevented. Colorectal: ACA more cost-effective up to a wound infection cost of >£1519 Combined: ACA more cost-effective up to a wound infection cost of >£500 Gynaecological: ACA more cost-effective up to a wound infection cost of >£81, <£430	Handling of resistance: Not mentioned Risk of confounding: Low Costs attributable to infection: "Cost per wound infection" from UK published data Sensitivity analysis: Varied costs due to infection, ICER sensitive to this parameter Other comments: Incomplete costs
Fried, 1996, <sup>62</sup> USA, RCT	Comparators: Single-dose intramuscular gentamicin (n = 72) vs culture-specific oral (n = 70) Length of prophylaxis: single dose	Surgery: Cystometrogram Patient group: Adults in a rehabilitation hospital	I <sup>Y</sup> or 2 <sup>Y</sup> : 1 <sup>Y</sup> Perspective: Secondary care (incomplete) Costs: Antibiotic costs Outcomes: Infections Definition of infection: Clinical signs of UTIs ADRs: Not reported Length of follow-up: Hospital stay	Difference in effect: Similar efficacy Difference in cost: Gentamicin is cheaper ICER: Not reported	Handling of resistance: Not reported Risk of confounding: Moderate Costs attributable to infection: Not reported Sensitivity analysis: Not reported Other comments: Incomplete costs

continued

TABLE 11 Summary of the economic evaluations identified in the review of non-glycopeptide antibiotics prophylaxis for surgery (cont'd)

Author, year, country of origin, study design	Alternatives under investigation (n)	Surgery and patient group	Methods used (primary or secondary economic analysis)	Results	Comments
Pearson, 1996, <sup>41</sup> UK, RCT (patients used either left or right ear as control)	Comparators: Sofradex eardrops vs no eardrops (n = 165) Length of prophylaxis: Three times per day for 5 days	Surgery: Bilateral grommet insertion Patient group: Children and adults	1 <sup>Y</sup> or 2 <sup>Y</sup> : 1 <sup>Y</sup> Perspective: Not clear Costs: No costs reported Outcomes: Grommet function, otitis media Definition of infection: Not reported ADRs: None reported Length of follow-up: 3 months	Difference in effect: No difference Difference in cost: No costs ICER: No ICER	Handling of resistance: None Risk of confounding: Low Costs attributable to infection: Not reported Sensitivity analysis: None reported Other comments: Not an economic evaluation
Pestotnik, 1996, <sup>53</sup> USA, large clinical series	Comparators: Normal practice vs computer-assisted decision support for antibiotic prophylaxis guidelines (n = 63759 out of 162,196) Length of prophylaxis: Variable	Surgery: Multiple Patient group: Multiple	1 <sup>Y</sup> or 2 <sup>Y</sup> : 1 <sup>Y</sup> Perspective: Hospital Costs: Antibiotic costs per patient and per treated patient Outcomes: Timing of 1st dose, ADRs, resistance, length of stay, mortality Definition of infection: Not reported ADRs: Recorded, but no details given Length of follow-up: Not stated	Difference in effect: Between 1985 and 1994, correct timing of 1st dose rose from 40 to 99.1%, ADRs reduced from 26.9 to 18.8%, resistance did not change, length of stay did not change, mortality reduced from 3.65 to 2.65% Difference in cost: Costs per treated patients reduced from \$122.66 to \$51.90 ICER: No ICER	Handling of resistance: Reported observed levels only Risk of confounding: High, no controlling for temporal effects on outcomes or costs Costs attributable to infection: Not reported Sensitivity analysis: Not reported
Schwartz, 1996, <sup>54</sup> USA, RCT (pseudo)	Comparators: Ofloxacin orally (n = 10) vs gentamicin and cephalosolin/gentamicin i.v. followed by cephadrine orally (n = 10) Length of prophylaxis: Started 2 h before surgery, continued for 7 days	Surgery: Penile prosthesis implants Patient group: Adult men	1 <sup>Y</sup> or 2 <sup>Y</sup> : 1 <sup>Y</sup> Perspective: Hospital Costs: Individual patient cost from hospital billing, only antibiotics and days in hospital Outcomes: MIC, surgical site infection rates Definition of infection: Not reported ADRs: Reported in one patient Length of follow-up: 8–21 months	Difference in effect: None Difference in cost: \$29,057 savings for 20 patients (not \$250,000 as reported) ICER: CMA	Handling of resistance: Not considered Risk of confounding: Moderate Costs attributable to infection: Calculated from antibiotics and hospital stay: \$29,057 savings for 20 patients (not \$250,000 as reported) Sensitivity analysis: Not reported Other comments: Prolonged prophylaxis. Incomplete costs (error in cost savings)

continued

TABLE 11 Summary of the economic evaluations identified in the review of non-glycopeptide antibiotics prophylaxis for surgery (cont'd)

Author, year, country of origin, study design	Alternatives under investigation (n)	Surgery and patient group	Methods used (primary or secondary economic analysis)	Results	Comments
VandenBergh, 1996, <sup>43</sup> The Netherlands, historical control	Comparators: Mupirocin nasal ointment (n = 868) vs nothing (n = 928) Length of prophylaxis: b.d. for 5 days	Surgery: Cardiothoracic Patient group: No details	1 <sup>Y</sup> or 2 <sup>Y</sup> : 1 <sup>Y</sup> Perspective: Hospital Costs: Individual patient cost from medical notes Outcomes: (Incisional or deep) surgical site infection rates Definition of infection: Not reported ADRs: Not reported Length of follow-up: Hospital stay	Difference in effect: Post-operative SSI rate: intervention 2.8% vs control 7.3% Difference in cost: ICER: \$16,333 saved per SSI prevented	Handling of resistance: Not mentioned Risk of confounding: High Costs attributable to infection: Calculated SSI attributable costs (extra days attributable judged by researchers) Sensitivity analysis: Varied SSIs from 1 to 100% (?). SSI attributable costs from 0 to 200% of observed costs of patients with an SSI. Cost of mupirocin from \$0 to \$1000 (?), actual cost: \$11). ICERs most sensitive to SSI-attributable costs Other comments: Prolonged prophylaxis. Incomplete costs. ICER: cost per surgical site infection prevented, but not incremental between the two alternatives in the study
Heit, 1997, <sup>59</sup> USA, RCT	Comparators: Ceftriaxone 1 g daily vs 2 MU penicillin G every 4 h Length of prophylaxis: Began day before surgery and continued until the day after surgery (n = 90)	Surgery: Oral/maxillofacial surgery Patient group: Compound mandibular fracture	1 <sup>Y</sup> or 2 <sup>Y</sup> : 1 <sup>Y</sup> Perspective: Secondary care Costs: Costs of drug administration Outcomes: Infection rates Definition of infection: Clinical evidence ADRs: Not reported Length of follow-up: 8 weeks	Difference in effect: No difference Difference in cost: Penicillin costs \$132 more per patient ICER: None reported	Handling of resistance: None reported Risk of confounding: Low Costs attributable to infection: None reported Sensitivity analysis: None reported Other comments: Incomplete costs

continued



TABLE 11 Summary of the economic evaluations identified in the review of non-glycopeptide antibiotics prophylaxis for surgery (cont'd)

Author, year, country of origin, study design	Alternatives under investigation (n)	Surgery and patient group	Methods used (primary or secondary economic analysis)	Results	Comments
Pearle, 1997, <sup>44</sup> USA, meta-analysis of 8 RCTs (n = 885) and 6 clinical series (n = 597)	Comparators: Placebo vs a range of active comparators Length of prophylaxis: Ranged from stat doses to 4-day course	Surgery: Shockwave lithotripsy Patient group: Not clear	1 <sup>Y</sup> or 2 <sup>Y</sup> ; 2 <sup>Y</sup> Perspective: Secondary care Costs: Drug costs, plus hospital charges for a UTI-related stay Outcomes: UTIs Definition of infection: Varied ADRs: Not reported Length of follow-up: Hospital stay	Difference in effect: Post-shockwave lithotripsy UTI placebo: 0–28%. Active: 0–7.7% Difference in cost: Depends on active placebo ICER: not reported	Handling of resistance: Not reported Risk of confounding: Low Costs attributable to infection: From hospital charges Sensitivity analysis: Threshold analysis shows that prophylaxis is cost-effective when treatment of a UTI is over £50 Other comments: Incomplete costs
Schilling, 1997, <sup>45</sup> Greece, retrospective cohort	Comparators: 2nd generation cephalosporin vs placebo (n = 132) Group A: needed prophylaxis, got it Group B: did not need prophylaxis, did not get it Group C: needed prophylaxis, did not get it Group D: did not need prophylaxis, got it Length of prophylaxis: Stat dose preoperatively	Surgery: Gastroduodenal surgery Patient group: Adults	1 <sup>Y</sup> or 2 <sup>Y</sup> ; 2 <sup>Y</sup> Perspective: Secondary care Costs: Not reported Outcomes: Infection rates, hospitalisation, mortality Definition of infection: Clinical or microbiological diagnosis ADRs: Not reported Length of follow-up: Length of hospital stay	Difference in effect: Mortality and hospital stay higher in inappropriate prophylaxis group Difference in cost: Not reported ICER: Not reported	Handling of resistance: Not reported Risk of confounding: High Costs attributable to infection: Not reported Sensitivity analysis: Not reported Other comments: No costs reported, only resource use reported
Wieck, 1997, <sup>46</sup> USA, RCT	Comparators: Cephazolin 1 g (n = 199) vs placebo (n = 238) Length of prophylaxis: Stat dose preoperatively	Surgery: Arthroscopic diagnostic and operative procedures Patient group: Adults and children	1 <sup>Y</sup> or 2 <sup>Y</sup> ; 1 <sup>Y</sup> Perspective: Secondary care Costs: Costs of drugs only Outcomes: Infections Definition of infection: Clinical diagnosis ADRs: Allergic reactions Length of follow-up: 6 weeks	Difference in effect: No difference Difference in cost: Not reported ICER: Not reported	Handling of resistance: Not reported Risk of confounding: Low Costs attributable to infection: Not reported Sensitivity analysis: Not reported Other comments: Incomplete costs

continued

TABLE 11 Summary of the economic evaluations identified in the review of non-glycopeptide antibiotics prophylaxis for surgery (cont'd)

Author, year, country of origin, study design	Alternatives under investigation (n)	Surgery and patient group	Methods used (primary or secondary economic analysis)	Results	Comments
Bold, 1998, <sup>47</sup> USA, RCT	Comparators: Cefonicid vs placebo Length of prophylaxis: Stat dose	Surgery: Axillary lymph node dissection Patient group: Adults (n = 178)	I <sup>Y</sup> or 2 <sup>Y</sup> : I <sup>Y</sup> Perspective: Secondary care Costs: Patient charges Outcomes: Infection Definition of infection: Locoregional signs of infection ADRs: Not reported Length of follow-up: 4 weeks	Difference in effect: Infection rate: cefonicid 6%, placebo 13%. Decreased infections leading to increased hospitalisation Difference in cost: cefonicid \$49.80, placebo \$364.87 ICER: None reported	Handling of resistance: None Risk of confounding: Low Costs attributable to infection: Costs calculated per patient Sensitivity analysis: None reported Other comments: Costs estimated per patient
Kapoor, 1998, <sup>48</sup> USA, RCT	Comparators: Ciprofloxacin 500 mg orally (n = 227) vs placebo (n = 230) Length of prophylaxis: Stat dose	Surgery: Transrectal prostate biopsy Patient group: Adults	I <sup>Y</sup> or 2 <sup>Y</sup> : I <sup>Y</sup> Perspective: Secondary care Costs: Patient charges Outcomes: Bacteruria, UTIs Definition of infection: Clinical definition ADRs: ADRs recorded Length of follow-up: Not clear	Difference in effect: UTIs requiring hospitalisation: placebo 2%, ciprofloxacin 0 Difference in cost: ciprofloxacin reduced the expected treatment cost of infectious complications by \$26 ICER: Not reported	Handling of resistance: Not reported Risk of confounding: Low Costs attributable to infection: Ciprofloxacin reduced the expected treatment cost of infectious complications by \$26 Sensitivity analysis: Not reported Other comments: Not full economic evaluation
Thomas, 1999, <sup>56</sup> Italy, double-blind RCT	Comparators: Ceftriaxone 2 g (n = 883) vs ceftazidime 2 g (n = 883) Length of prophylaxis: Single dose at induction	Surgery: Breast women not on adjuvant chemotherapy	I <sup>Y</sup> or 2 <sup>Y</sup> : I <sup>Y</sup> Perspective: Hospital Costs: Antibiotics, dressings and associated nursing time, hotel costs for infected patients only (source not stated) Outcomes: Wound infection, overall infections Definition of infection: Clinical signs of inflammation ADRs: None reported Length of follow-up: 4 weeks	Difference in effect: Wound infections: ceftriaxone 3.4%, ceftazidime 7.7%. Wound infection where bacteria grown: ceftriaxone 0.45%, ceftazidime 0.91% Difference in cost: ceftriaxone \$99, ceftazidime \$199. Net saving per patient: \$100 ICER: No ICER	Handling of resistance: Not reported Risk of confounding: Low Costs attributable to infection: Hotel, dressings and antibiotic costs attributed to infection, but not clear where these data are from Sensitivity analysis: Not reported Other comments: Incomplete costs

continued

TABLE 11 Summary of the economic evaluations identified in the review of non-glycopeptide antibiotics prophylaxis for surgery (cont'd)

Author, year, country of origin, study design	Alternatives under investigation (n)	Surgery and patient group	Methods used (primary or secondary economic analysis)	Results	Comments
Kulling, 2000, <sup>49</sup> USA, decision analysis	Comparators: Antibiotics vs placebo Length of prophylaxis: varied, not clear	Surgery: Percutaneous endoscopic gastrostomy Patient group: Not stated	1 <sup>st</sup> or 2 <sup>nd</sup> : 2 <sup>nd</sup> . Pooled effectiveness data from 7 trials for multiple alternatives to placebo Perspective: Secondary care Costs: Estimates and patient charges Outcomes: Wound infection rates Definition of infection: Clinical wound infection ADRs: Not reported Length of follow-up: Not reported	Difference in effect: Infection rates lower with antibiotics Difference in cost: \$76.72 saved per percutaneous endoscopic gastrostomy ICER: Not reported	Handling of resistance: None reported Risk of confounding: Low Costs attributable to infection: From charges Sensitivity analysis: Tested effect of changing the costs attributable to infection, and the rate of infection Other comments: Threshold analysis of when cost of infection was equalled by cost of prophylaxis
Rau, 2000, <sup>57</sup> Germany, multi-centre (114) matched control	Comparators: Group A, ceftriaxone vs other cephalosporins (n = 672 pairs); Group B, ceftriaxone vs penicillins (n = 400 pairs), most had metronidazole added Length of prophylaxis: "Left to the practitioners", 90% ceftriaxone given as a single dose, average duration of other $\beta$ -lactams: 2–3 days	Surgery: Elective colon resection Patient group: Adults with no infection	1 <sup>st</sup> or 2 <sup>nd</sup> : 1 <sup>st</sup> Perspective: Secondary care Costs: Length of stay, antibiotics, mechanical ventilation, reoperation Outcomes: Local and systemic postoperative infection Definition of infection: Not reported ADRs: Not reported Length of follow-up: 10 days or hospital stay	Difference in effect: Local infection: Group A, 6.0 vs 6.5%; Group B, 4.0 vs 10.5%. Systemic infection: Group A, 4.9 vs 6.3%; Group B, 3.3 vs 10.5% Difference in cost: Group A, €160.7; Group B, €416.2. Length of stay: Group A, 16.2 vs 16.9 days; Group B, 15.8 vs 17.6 days (p < 0.001) ICER: Ceftriaxone dominant	Handling of resistance: None reported Risk of confounding: High, controlled for by regression. Age, concomitant disease affected systemic infection rates. Penicillin was a risk factor compared with ceftriaxone Costs attributable to infection: Not reported Sensitivity analysis: Not reported Other comments: Incomplete costs

ACA, amoxicillin/clavulanic acid; ASA, American Society of Anesthesiologists; CDC, Centers for Disease Control; CMA, cost-minimisation analysis; CRP, C-reactive protein; GI, gastrointestinal; ICU, intensive care unit; MIC, minimum inhibitory concentration; PONV, post-operative nausea and vomiting; SSI, surgical site infection; UTI, urinary tract infection; WBC, white blood cell count.

length of stay due to infection.<sup>42–44,47–52,54,56,57,61</sup> Extra length of stay due to infection is a dominating factor in costs. This was obtained in a range of ways, from direct measurement, use of published data or qualitative assessment about whether days in hospital were attributable to infection or not. The perspective was always the secondary care payer, when it could be determined.

Only four studies reported ICERs.<sup>43,44,49,52</sup> Only four studies reported sensitivity analysis, which suggested that costs attributable to infection had the most effect on the ICER.

There was no explicit modelling of resistance in any study, in either a static or dynamic model.

## Summary

In summary, the lessons learnt from this review are as follows:

- Outcomes need to be very clearly defined and better reported, including adverse drug events, differing severity of infection and causative organisms.
- The main cost driver (from the secondary care perspective) is length of stay changes caused by infection. This needs to be measured directly and data should be corrected for confounding factors.
- Antibiotic resistance has not been considered explicitly so far.

The impact of surgical infections on costs post-discharge and patient QoL has not been considered so far.

## Economic evaluations of antibiotics where antibiotic resistance is a problem

### Introduction

The purpose of this review was to characterise the methods used to deal with resistance in economic evaluations of antibiotics. Due to the lack of explicit modelling of resistance in economic evaluations in surgical antibiotic prophylaxis, a wider set of studies were examined, including all anti-infective agents.

### Methods

#### Inclusion criteria

Studies that were full economic evaluations were considered, that is: (1) cost-effectiveness evaluations, including cost-minimisation and

cost–consequence analyses; (2) cost–utility analyses; and (3) cost–benefit analyses.<sup>34</sup> Studies evaluated antibiotics and could include evaluations of antibiotic treatment or antibiotic prophylaxis for any medical use.

#### Data extraction and quality assessment

Data were extracted on key components of standard economic evaluations including data on the comparators, whether the study was based on primary or secondary economic analysis data, the perspective, the costs and outcomes measured, the length of follow-up, how antibiotic resistance was handled, estimates of incremental cost-effectiveness and the risk of confounding and any costs attributable to infection.

## Results

Resistance has been examined almost exclusively in the anti-infective management of HIV, malaria and tuberculosis (TB). The studies found were examined to obtain further guidance and ideas as to what methodological approach to employ in seeking to model the impact of antibiotic resistance.

Based on the 43 papers that were obtained through the search undertaken for this review, it was found that resistance appears to be handled differently between different infections. Hence this review is reported by type of infection. This reflects the different mechanisms of resistance, and the relative importance of primary and secondary resistance in treatment failure. *Table 12* provides summary details of the included studies.

## Discussion

### HIV

In HIV, both primary and secondary resistance are key issues in economic evaluations. Resistance develops within an individual patient during treatment, leading to treatment failure and the need to switch to another regimen. Also, treatment-naïve patients can present with resistant HIV strains, referred to as primary resistance. Based on the review, three economic evaluations in HIV consider resistance. All three trials used lifetime Markov modelling. In the two US and one German HIV trials, resistance is only considered as a main component of ‘treatment failure’, so is considered important in determining whether a patient needs to go on to another regimen,<sup>63</sup> or the relative cost-effectiveness of genotypic antiretroviral resistance testing.<sup>64,65</sup> Varying efficacy of HIV highly active anti-retroviral therapy (HAART) from 2 to 50 years (i.e. the effect of change in efficacy due to drug resistance)

TABLE 12 Summary of economic evaluations found in the review of antibiotics when antimicrobial resistance is a problem

Author, year, country of origin	Alternatives under investigation and patient group	Methods used (primary or secondary economic analysis)	Handling of resistance	Results	Comments
Simpson, 2004, <sup>63</sup> USA	<b>HIV:</b> lopinavir/ritonavir vs nelfinavir for 1-line HAART in combination with stavudine/lamivudine	<i>I<sup>v</sup></i> or <i>2<sup>v</sup></i> : Markov model, 12 mutually exclusive and jointly exhaustive states (HIV events and opportunistic infections) <i>Perspective:</i> Healthcare system <i>Costs:</i> Medicaid charge data <i>Outcomes:</i> Viral load and CD4 count data from 48-week trial, EQ-5D attached to health states <i>Length of follow-up:</i> Until 50% patients had died; discount for costs and QALYs: 3%	Base case did not consider resistance. Sensitivity analysis assumed protease inhibitor resistance would incur a cost, so LPV/r would be dominant. The basis for this assumption and sources of figures are not reported. No long-term consideration of transmission of resistance	<i>Difference in effect:</i> Median estimated time on 1st regimen: LPV/r 962 days, nelfinavir 837 days <i>Difference in cost:</i> LPV/r would save \$3461 over the first 5 years <i>ICER:</i> Cost per QALY: \$6653	<i>Risk of confounding:</i> Low Costs attributable to infection: Charges
Weinstein, 2001, <sup>64</sup> USA	<b>HIV screening:</b> GART vs clinical judgement in (1) 1st treatment failure, (2) before 1st treatment	<i>I<sup>v</sup></i> or <i>2<sup>v</sup></i> : Markov model, 6 states (HIV events and opportunistic infections) <i>Perspective:</i> Societal <i>Costs:</i> National charges <i>Outcomes:</i> Viral load, CD4, quality-adjusted life expectancy, trial-based data for drug failure <i>Length of follow-up:</i> Lifetime of 1 m patients; discount for costs and QALYs: 3%	Assumed drug failure at 24 months, and in sensitivity analysis, tested effect of longer durations of efficacy Cost per QALY not changed very much up to 50 yr efficacy Primary resistance considered in sensitivity analysis, this would increase the case for genotypic testing, and would reduce the cost per QALY No long-term consideration of transmission of resistance	<i>Difference in effect:</i> Discounted QALE without GART 60.9 months; with GART 63.1 months <i>Difference in cost:</i> Discounted incremental cost: \$3300 <i>ICER:</i> base case: \$17,900 or \$16,300 per QALY depending on trial data used	<i>Risk of confounding:</i> Low Costs attributable to infection: Charge Other comments: Estimated probability of infection as a function of CD4 count

continued

TABLE 12 Summary of economic evaluations found in the review of antibiotics when antimicrobial resistance is a problem (cont'd)

Author, year, country of origin	Alternatives under investigation and patient group	Methods used (primary or secondary economic analysis)	Handling of resistance	Results	Comments
Corzilius, 2004, <sup>65</sup> Germany	<b>HIV screening:</b> GART vs clinical judgement in (1) treatment failure, (2) before 1st treatment	<i>I<sup>IV</sup></i> or <i>2<sup>IV</sup></i> : Markov model, 6 states (HIV events and opportunistic infections) <i>Perspective:</i> Healthcare system <i>Costs:</i> Mix of German charges and UK research data. <i>Outcomes:</i> Life-years gained <i>Length of follow-up:</i> Discount for costs and QALYs: 5%	Primary resistance considered in additional analysis, this would increase the case for genotypic testing if probability of HAART failure was reduced by 36% No long-term consideration of transmission of resistance	<i>Difference in effect:</i> GART after treatment failure increased life expectancy by 9 months <i>Difference in cost:</i> GART after treatment failure increased undiscounted costs by €16,406 <i>ICER:</i> Discounted cost per LYG: €22,510	<i>Risk of confounding:</i> Low <i>Costs attributable to infection:</i> Published sources <i>Other comments:</i> GART prior to initiation of HAART would be equally cost-effective if probability of HAART failure was reduced by 36%
Sudre, 1992, <sup>66</sup> USA	<b>Malaria:</b> Chloroquine (Cq) vs amodiaquine (Aq) vs pyrimethamine/sulfadoxine (PS) to treat malaria in sub-Saharan children 6–59 months old	<i>I<sup>IV</sup></i> or <i>2<sup>IV</sup></i> : Decision analytic model, where failure was caused by resistance, ADRs or non-compliance <i>Perspective:</i> Healthcare system <i>Costs:</i> Purchase costs of drugs only <i>Outcomes:</i> Drug efficacy in clearing parasitaemia, mortality <i>Length of follow-up:</i> One febrile episode	Three situations modelled: no Cq resistance; low Cq, low Aq resistance; high Cq, moderate Aq resistance. Decision analytic model incorporated probability of 4 levels of response to a drug (R0, R1, RII, RIII), and associated mortality, for each of these three situations. Threshold analysis of which level of CRPF Aq or PS would be more cost-effective than Cq. No long-term consideration of transmission of resistance	<i>ICER:</i> Multiple ICERs. At all levels of resistance, for number of deaths prevented, Aq and PS are more cost effective than Cq	<i>Risk of confounding:</i> Low <i>Costs attributable to infection:</i> Not included in the model <i>Other comments:</i> Incomplete costs. Increased compliance had a major effect on reducing ICERs
Goodman, 2001, <sup>67</sup> UK	<b>Malaria:</b> Chloroquine (Cq) vs pyrimethamine/sulfadoxine (PS) to prevent malaria in sub-Saharan primigravidae	<i>I<sup>IV</sup></i> or <i>2<sup>IV</sup></i> : Decision analytic model with PSA in a low, middle or higher income country <i>Perspective:</i> Healthcare system <i>Costs:</i> Published sources <i>Outcomes:</i> From Cochrane meta-analysis: birthweight, mortality, discounted years of life lost (DYLLs) <i>Length of follow-up:</i> Lifetime	Threshold analysis of which level of CRPF PS would be more cost-effective than Cq. No long-term consideration of transmission of resistance	<i>ICER:</i> Multiple ICERs. Intervention more cost-effective in higher income countries as life expectancy was higher at birth	<i>Risk of confounding:</i> Low <i>Costs attributable to infection:</i> Included detailed costs <i>Other comments:</i> Estimated probability of neonatal mortality as a function of birthweight, converted mortality to DYLLs

continued

TABLE 12 Summary of economic evaluations found in the review of antibiotics when antimicrobial resistance is a problem (cont'd)

Author, year, country of origin	Alternatives under investigation and patient group	Methods used (primary or secondary economic analysis)	Handling of resistance	Results	Comments
Goodman, 2001, <sup>68</sup> UK	<b>Malaria:</b> Chloroquine (Cq) vs pyrimethamine/sulfadoxine (PS) to treat malaria in sub-Saharan presenting with uncomplicated malaria	<i>I<sup>Y</sup></i> or <i>2<sup>Y</sup></i> : decision-analytic model with PSA in an area of low income and high transmission Perspective: healthcare system Costs: published charges Outcomes: death, recovery with or without neurological sequelae, DALYs Length of follow-up: lifetime, discount for costs and DALYs: 5%	Threshold analysis of which level of CRPF PS would be more cost-effective than Cq. Changing Cq to PS as the first-line drug was modelled over 10 years to find the optimal year of switch. Model run assuming: resistance stayed constant for 10 years; resistance grew 11% per year (from a published source). Compared switching at 1 year with 9 years, or not switching, etc.	ICER: Multiple ICERs. Optimal year of switch was dependent on initial level of resistance, resistance growth rates and decision-makers' time preference	Risk of confounding: Low Costs attributable to infection: Published sources Other comments: Incorporated estimates of compliance. Could not provide a definitive level at which to switch drugs
Coleman, 2004, <sup>69</sup> UK	<b>Malaria:</b> Artemisinin-based treatment (ACT) vs current therapy in sub-Saharan Africa	<i>I<sup>Y</sup></i> or <i>2<sup>Y</sup></i> : <i>2<sup>Y</sup></i> decision analytic model with Monte Carlo run over 10 years, threshold analysis Perspective: Healthcare system Costs: Published charges Outcomes: DALYs Length of follow-up: Lifetime, discount for costs and DALYs: 3%	General logistic growth function, at which starting resistance and growth was varied. Starting resistance assumed (authors' estimate) to be 0.1% (low estimate) and 1% (high estimate), varied 9 times for current therapy Period of time for model: 10 years (varied from 5 to 15 years) Varied the ratio of resistance in ACT: current therapy 16 times	ICER: Multiple ICERs. Results showed that ACTs are more than 95% likely to be cost-effective under most conditions, where cost-effectiveness was defined as cost per DALY of less than \$150. The condition where they were not cost-effective was when resistance to current therapy was lowest	Risk of confounding: Low Costs attributable to infection: Published sources Other comments: Compliance handled in the model, incorporated into probability of therapy success

continued

TABLE 12 Summary of economic evaluations found in the review of antibiotics when antimicrobial resistance is a problem (cont'd)

Author, year, country of origin	Alternatives under investigation and patient group	Methods used (primary or secondary economic analysis)	Handling of resistance	Results	Comments
Brewer, 1998, <sup>70</sup> USA	<b>Tuberculosis:</b> Empirical standard treatment vs empirical multidrug resistant (MDR) treatment vs no treatment until positive culture, in HIV-negative and HIV-positive patients	<i>I<sup>v</sup></i> or <i>2<sup>v</sup></i> : Decision analytic model Perspective: Healthcare system Costs: Drugs, screening, ADRs (hepatitis), treatment failure, hospital stay Outcomes: Mortality, mortality associated with MDR TB was assumed to be the same as for standard strains of TB Length of follow-up: Assumed to be end of treatment	Different levels of MDR TB incidence tested in sensitivity analysis, varied from 0.0001 to 0.139, rates taken from a published US survey. Threshold analysis (not completely reported) suggests that empirical MDR treatment is "cost-effective" where MDR TB rates exceed 9.6%. No long term consideration of transmission of resistance	<i>Difference in effect:</i> Using empirical MDR treatment instead of waiting for culture results increased mortality by 2% <i>Difference in cost:</i> Empirical multiple drug-resistant antituberculous chemotherapy costs on average less than \$3 more per patient evaluated ICER: Empirical standard treatment versus no treatment until positive culture: \$1,104,000 per death averted. In HIV patients, empirical MDR treatment versus no treatment until positive culture: \$8000	<i>Risk of confounding:</i> Low Costs attributable to infection: From published sources <i>Other comments:</i> Probability of drug treatment ADRs incorporated into model, with attributable costs and mortality. Compliance assumed to be 100%
Weis, 1999, <sup>71</sup> USA	<b>Tuberculosis:</b> DOT ( <i>n</i> = 402) vs historical control: traditional care ( <i>n</i> = 257)	<i>I<sup>v</sup></i> or <i>2<sup>v</sup></i> : <i>I<sup>v</sup></i> cost-consequences study Perspective: HMO provider Costs: Patient-based retrospective medical note examination: consumables, equipment, labour, overheads; Texas list charges 1995 Outcomes: Therapy duration, relapse rates Length of follow-up: Not clear (duration of therapy?)	DOT led to a reduction in acquired resistance from 5.1 to 0.5% ( <i>p</i> < 0.001). No long-term consideration of transmission of resistance	<i>Difference in effect:</i> Therapy duration: intervention, 334 days; control, 550 days ( <i>p</i> < 0.001). Relapse rates: intervention, 1%; control, 4.3% ( <i>p</i> = 0.0013) <i>Difference in cost:</i> Total cost per patient: intervention, \$11,260; control, \$27,630 ( <i>p</i> < 0.001) ICER: Not reported	<i>Risk of confounding:</i> High Costs attributable to infection: Patient charges
Drobniewski, 2000, <sup>72</sup> UK	<b>Tuberculosis screening:</b> National rapid molecular TB screening service ( <i>n</i> = 55). Cohort study (not clear who control was)	<i>I<sup>v</sup></i> or <i>2<sup>v</sup></i> : <i>I<sup>v</sup></i> Perspective: Healthcare system (secondary care) Costs: TB treatment costs, inpatient stays, outpatient visits Outcomes: Mortality (no deaths occurred) Length of follow-up: 6 months	No long-term consideration of transmission of resistance	<i>Difference in effect:</i> 28 days to initiation of treatment were saved by the screening service <i>Difference in cost:</i> Screening service reduced costs of negative pressure isolation room by £50,000 to £150,000 ICER: Not reported	<i>Risk of confounding:</i> Very high Costs attributable to infection: Estimated from change in use of negative pressure isolation room <i>Other comments:</i> Not clear how patients were included. Incomplete costs

continued



TABLE 12 Summary of economic evaluations found in the review of antibiotics when antimicrobial resistance is a problem (cont'd)

Author, year, country of origin	Alternatives under investigation and patient group	Methods used (primary or secondary economic analysis)	Handling of resistance	Results	Comments
Suarez, 2002, <sup>73</sup> Peru	<b>Tuberculosis:</b> (1) DOT MDR regimen for 18 months vs (2) DOT MDR plus individualised treatment for failures vs (3) DOT MDR plus new individualised treatment for failures based on MDR sensitivity. All 3 compared with just using isoniazid monotherapy. Cohort study	<i>I<sup>TV</sup></i> or <i>2<sup>TV</sup></i> : <i>I<sup>TV</sup></i> data mixed with published data: overall: <i>2<sup>TV</sup></i> , with PSA modelling for outcomes and ranges <i>Perspective:</i> Healthcare system <i>Costs:</i> TB treatment costs, inpatient stays, outpatient visits (published sources) <i>Outcomes:</i> Long-term cure rate, mortality, DALY <i>Length of follow-up:</i> Lifetime	Resistance to regimens handled by using published "non-response" rates Examined effect of impact of treatment on transmission: reproduction number (number of secondary cases produced by primary case in the next generation), based on published sources; generation time (years) based on published sources; duration of infectiousness in presence or absence of MDR regimens, based on published sources and authors' assumptions	<i>ICER:</i> Mean cost per DALY (a) excluding transmission benefits, (b) including transmission benefits: isoniazid vs (1): (a) \$270 (95% CI 178 to 415); (b) \$211 (95% CI 126 to 339) isoniazid vs (2): (a) \$493 (95% CI 350 to 701); (b) \$368 (95% CI 227 to 556) isoniazid vs (3): (a) \$672 (95% CI 474 to 947); (b) \$484 (95% CI 285 to 737) <i>ICERs</i> lower when transmission benefits included	Risk of confounding: Low Costs attributable to infection: Published sources
Sterling, 2003, <sup>74</sup> USA	<b>Tuberculosis:</b> DOT vs DOT-plus in smear-positive pulmonary TB	<i>I<sup>TV</sup></i> or <i>2<sup>TV</sup></i> : <i>2<sup>TV</sup></i> Markov decision analytic model with Monte Carlo simulation (10 years, 1-year cycle, 25,000 Monte Carlo simulations), no ranges for probabilities <i>Perspective:</i> Healthcare provider <i>Costs:</i> Drugs and tests <i>Outcomes:</i> Deaths over 10 years <i>Length of follow-up:</i> 10 years	High (10%) and intermediate (3%) proportions of MDR, but assumed resistance stayed the same over a period of 10 years	<i>Difference in effect:</i> DOTs: 276 deaths (24 MDR), DOTs-plus (optimal use) in an area with 3% primary MDR: 4 fewer deaths. DOTs-plus (optimal use) in an area with 10% primary MDR: 28 fewer deaths <i>ICER:</i> 3% resistance, \$68,800 per death averted; 10% resistance, \$8580 per death averted	Risk of confounding: Low Costs attributable to infection: Not clear, incomplete (drugs and tests only)

continued

TABLE 12 Summary of economic evaluations found in the review of antibiotics when antimicrobial resistance is a problem (cont'd)

Author, year, country of origin	Alternatives under investigation and patient group	Methods used (primary or secondary economic analysis)	Handling of resistance	Results	Comments
Sharpe, 2005, <sup>75</sup> USA	<b>MRSA resistance:</b> Oral linezolid (n = 30) vs intravenous vancomycin (n = 30) in the treatment of MRSA-complicated, lower extremity skin and soft-tissue infections in adults, treatment for 7–21 days	<i>I<sup>IV</sup></i> or <i>2<sup>IV</sup></i> : <i>I<sup>IV</sup></i> Perspective: Healthcare provider Costs: Inpatient charges Outcomes: Clinical cure Length of follow-up: Treatment was administered for 7–21 days. Clinical and microbiological tests of cure carried out 10 days after end of therapy	No long-term consideration of transmission of resistance	<b>Difference in effect:</b> Better clinical cure and shorter length of stay with linezolid <b>Difference in cost:</b> Inpatient medication charges \$117 less for vancomycin. Inpatient stay charges \$6438 less for linezolid. Outpatient charges \$388 less for linezolid ICER: Not reported	Risk of confounding: Very high (industry funded, method of randomisation not reported, open label) Costs attributable to infection: Patient charges
VandenBergh, 1996, <sup>43</sup> The Netherlands	<b>MRSA resistance:</b> Mupirocin nasal ointment (n = 868) vs nothing (n = 928) in cardiothoracic surgery b.d. for 5 days	<i>I<sup>IV</sup></i> or <i>2<sup>IV</sup></i> : <i>I<sup>IV</sup></i> Perspective: Hospital Costs: Individual patient cost from medical notes Outcomes: (Incisional or deep) surgical site infection rates Length of follow-up: Hospital stay	No long-term consideration of transmission of resistance	<b>Difference in effect:</b> Postoperative SSI rate: intervention 2.8% vs control 7.3% <b>Difference in cost:</b> Not reported ICER: \$16,333 saved per SSI prevented	Risk of confounding: High Costs attributable to infection: Calculated SSI-attributable costs (extra days attributable judged by researchers)

CRPE, chloroquine resistant *Plasmodium falciparum*; DALY, disability-adjusted life-year; DOT, directly observed therapy; GART, genotypic antiretroviral resistance testing; HAART, highly active antiretroviral therapy; HMO, Health Maintenance Organisation; LPV/r, lopinavir/ritonavir; LYG, life-year gained; MDR, multi-drug resistance; PSA, probabilistic sensitivity analysis; QALE, quality-adjusted life expectancy.

only changed the discounted cost per QALY from US\$17,900 to US\$19,900.<sup>64</sup> Primary resistance was considered in Weinstein and colleagues' HIV screening model, in the sensitivity analysis.<sup>64</sup> This would increase the case for genotypic testing, and would reduce the cost per QALY. It is also considered by Corzillius and colleagues,<sup>65</sup> to assess a level of resistance at which screening would be important. There is no long term consideration of transmission of resistance in any of these HIV trials, despite the increasing importance of transmission of primary resistance, and associated failure of first-line HAART.<sup>63-65</sup> There was also no attempt to examine the potential effects of an increase in resistance over time. Compliance was not considered, so was evidently assumed to be 100%, although this is a factor in increasing secondary resistance.

### **Malaria**

In malaria, the key resistance issue is widespread primary resistance of *Plasmodium falciparum* to many antimalarial agents. Resistance does not develop within an individual during treatment, but primary resistant strains are transmitted between patients, leading to treatment failure and the need to switch to another regimen. Therefore, resistance is considered as a main component of treatment failure, and levels of resistance in a population predicate empirical first-line treatment. Four economic evaluations in malaria consider resistance.<sup>66-69</sup>

Sudre and colleagues<sup>66</sup> modelled three levels of drug resistance, and their decision analytic model incorporated the probability of four levels of response to a drug (R0, RI, RII, RIII), and associated mortality, for each of these three situations. They carried out a threshold analysis of which level of chloroquine-resistant *Plasmodium falciparum* (CRPF) would change which drug was cost-effective. Increased compliance to drugs had a large impact on reducing ICERs. Goodman and colleagues also carried out a threshold analysis of the level of CRPF at which one antimalarial would be more cost-effective than another.<sup>67</sup>

Goodman and colleagues<sup>68</sup> carried out a threshold analysis to determine at which level of CRPF pyrimethamine/sulfadoxine would be more cost-effective than chloroquine. Changing chloroquine to pyrimethamine/sulfadoxine as the first-line drug was modelled over 10 years to find the optimal year of switch. The model was run assuming that (1) resistance stayed constant for 10 years and (2) resistance grew at 11% per year.

The authors compared switching at 1 year with 9 years, or not switching, and so on, generating multiple ICERs. They were not able to identify an optimal year of switch, as it was dependent on initial level of resistance, resistance growth rates and decision-makers' time preference.

Coleman and colleagues<sup>69</sup> carried out a threshold analysis to determine at which level of CRPF artemisinin-based combination therapy (ACT) would be more cost-effective than pyrimethamine/sulfadoxine. Changing pyrimethamine/sulfadoxine to ACT as the first-line drug was modelled over 5, 10 and 15 years. A general logistic growth function was used to calculate the effect of increasing resistance over time, and starting resistance and growth were varied in the model. Starting resistance was assumed (authors' estimate) to be 0.1% (low estimate) and 1% (high estimate), and was varied nine times for pyrimethamine/sulfadoxine. The authors also varied the ratio of resistance in ACT to pyrimethamine/sulfadoxine 16 times. The results showed that ACT is more than 95% likely to be cost-effective under most conditions, where cost-effectiveness was defined as cost per disability-adjusted life-year (DALY) of less than US\$150. The condition where they were not cost-effective was when resistance to pyrimethamine/sulfadoxine was lowest.

There was no long-term consideration of transmission of resistance in any of the malaria studies. There was also no attempt to examine the potential effects of an increase in resistance over time in two studies.<sup>66,67</sup> Two studies attempted to predict the future trajectory of drug resistance, but rates of growth of resistance were assumptive rather than empirical data.<sup>68,69</sup> Compliance to drugs was not assumed to be 100% in all studies.<sup>66-69</sup>

### **Tuberculosis**

In TB, key resistance issues are both primary resistance, where treatment-naïve patients can present with resistant TB strains, and secondary resistance, where resistance develops during treatment, leading to treatment failure and the need to switch to another regimen. The incidence of multi-drug resistance (MDR) is increasing in all TB populations, particularly those who are also HIV positive. Five economic evaluations in TB consider resistance. In Brewer and colleagues,<sup>70</sup> the impact of different levels of MDR TB incidence was tested in sensitivity analysis, varied from 0.0001 to 0.139, rates being taken from a published US survey. Threshold analysis (not completely reported) suggests that empirical MDR

treatment is “cost-effective” where MDR TB rates exceed 9.6%. The probability of drug treatment ADRs was incorporated into the model, along with attributable costs and mortality. Mortality associated with MDR TB was assumed to be the same as for standard strains of TB. Using empirical MDR treatment instead of waiting for culture results increased mortality by 2%.

Directly observed therapy (DOT) is considered to reduce the emergence of MDR as improved compliance with the regimen prevents resistance developing within an individual patient during treatment. Weis and colleagues<sup>71</sup> compared the costs and effects of DOT with standard therapy and reported a reduction in acquired resistance from 5.1 to 0.5% ( $p < 0.001$ ).

Suarez and colleagues<sup>73</sup> compared three regimens with isoniazid monotherapy: (1) DOT MDR regimen for 18 months; (2) DOT MDR plus individualised treatment for failures; and (3) DOT MDR plus new individualised treatment for failures based on MDR sensitivity. Resistance to regimens was handled by using published ‘non-response’ rates. The authors also examined the effect of impact of treatment on transmission, using the following parameters: reproduction number (number of secondary cases produced by primary case in the next generation), based on published sources; generation time (years), based on published sources; and duration of infectiousness in presence or absence of MDR regimens, based on published sources and authors’ assumptions. ICERs (mean cost per DALY) were calculated excluding transmission benefits and including transmission benefits. ICERs were lower when transmission benefits were included.

Sterling and colleagues examined DOT versus DOT-plus in smear-positive pulmonary tuberculosis using a Markov decision analytic model with Monte Carlo simulation in a cohort over 10 years.<sup>74</sup> They examined the effect of high (10%) and intermediate (3%) proportions of MDR, but assumed that resistance stayed the same over a period of 10 years. ICERs (cost per death averted) were higher where MDR resistance levels were lower.

Three studies report that delays caused by waiting for a positive screen increased mortality.<sup>70–72</sup>

There was no long-term consideration of transmission of resistance in four TB studies.<sup>70–72,74</sup>

There was also no attempt to examine the potential effects of an increase in resistance over time in all studies.<sup>70–74</sup>

### MRSA resistance

Two economic evaluations in MRSA consider primary resistance in terms of treatment failure. Sharpe and colleagues examined oral linezolid ( $n = 30$ ) versus intravenous vancomycin ( $n = 30$ ) in the treatment of MRSA-complicated, lower extremity skin and soft-tissue infections in adults.<sup>75</sup> VandenBergh and colleagues examined mupirocin nasal ointment ( $n = 868$ ) versus nothing ( $n = 928$ ) in cardiothoracic surgery.<sup>43</sup> There was no long-term consideration of transmission of resistance in either study.

### Summary

In summary, the lessons learnt from this review are:

- *Resistance levels:* Most studies considered resistance as a component of treatment failure. Most studies only used estimates of initial levels of resistance rather than observed figures, only two TB studies used observed resistance rates.<sup>70,71</sup> Published non-response rates were used as an empirical measure of resistance in one study.<sup>73</sup>
- *Transmission of resistance:* Transmission effects were only examined in one study in TB, using reproduction numbers based on published sources, generation time (years) based on published sources and duration of infectiousness.<sup>73</sup>
- *Changes in resistance over time:* Increases in resistance over time were examined in two malaria studies only, and these increases were author estimates, not observed increases.<sup>68,69</sup>
- *Impact of intervention on resistance:* Only one study measured the effect of the intervention on resistance.<sup>71</sup>
- *Decision-makers’ time preference:* This affects the impact of resistance on the choice of optimal intervention.

For any particular microorganism, little is known about current levels of resistance, the rate of development of resistance transmission rates and the impact of interventions on resistance. The models presented in these evaluations are indicative only. They also take a relatively narrow perspective. Despite the longitudinal nature of some of these models, there is no incorporation of evidence regarding the societal impact caused by the adverse health effects of resistance.

## Use of epidemiological and decision analytic techniques to model antibiotic resistance

### Introduction

A selective review was undertaken based on published papers which provided examples of epidemiological and decision analytic techniques to model antibiotic resistance. The aim was to learn from innovative methodological approaches to the complex issue of modelling resistance. Ideally, modelling of resistance would allow us to obtain quantitative estimates of the change in the rate of resistance, and subsequent costs and consequences, arising from a decision to use glycopeptides prophylactically.

### Antibacterial resistance

Antibiotic resistance arises due to selection. Genetic mutations that confer resistance to antibiotics are selected for in the presence of antibiotics as antibiotic-sensitive organisms are removed from the population and antibiotic-resistant bacteria thrive. However, resistance to a particular antibiotic can develop in the absence of that antibiotic, due to the transmission of antibiotic-resistant bacteria between individuals, due to the existence of common modes of resistance across antibiotics and also due to the exchange of genetic material (plasmids and transposons) between bacteria. The increased incidence of antibiotic-resistant infections has led to increased morbidity and mortality associated with infection and is especially worrying in the light of the likely lack of new antibiotics in the near future.<sup>76,77</sup>

### Effect of prophylactic usage on the development of resistance

Although the widespread use of antibiotics, including their prophylactic use, has been identified as one factor leading to an increase in antibiotic resistance, it has been suggested that it is not axiomatic that the prophylactic use of antibiotics increases the total usage of antibiotics and rate at which resistance develops. In the *Effective Healthcare Bulletin* (<http://www.york.ac.uk/inst/crd/ehc45.htm>) entitled 'Antimicrobial prophylaxis in colorectal surgery', it was suggested that the "appropriate use of antimicrobial prophylaxis in colorectal surgery may help to reduce the development of antibiotic resistant bacteria" as "by preventing postoperative wound infection, single dose or short-term antibiotic prophylaxis can reduce the need for long-term antibiotic therapy and therefore may

contribute to reducing selection of antibiotic resistant bacteria". In a similar vein, the SIGN guideline entitled 'Antibiotic prophylaxis in surgery'<sup>3</sup> suggests as a possible cost-effectiveness decision rule that prophylaxis should be given if "it is likely to reduce overall antibiotic consumption the hospital" and goes on to suggest that prophylaxis is highly recommended if prophylaxis unequivocally reduces major morbidity, reduces hospital costs **and** [authors' emphasis] is likely to decrease overall consumption of antibiotics. However, it was suggested by consultees during the course of this project that the overall consumption of antibiotics was not a good proxy for risk of the development of resistance. Although the rate at which antibiotic resistance develops will increase as the usage and so the rate of exposure of bacteria to antibiotic increases, it will also be affected by therapeutic practice and patient characteristics, the presence of a large bacterial inoculum as a reservoir of resistant mutants and the use of insufficiently high drug doses may increase the rate of resistance.<sup>77,78</sup>

Specifically, it was suggested by the consultees that resistance may be more likely to develop where short prophylactic courses are used compared with longer therapeutic courses, even where the overall antibiotic usage is similar.

### Results

The models of antibiotic resistance identified during this review could be grouped (with examples) as follows.

#### **Models of the development of resistance in an experimental system**

De Gelder and colleagues developed mathematical models to explain the loss of resistance observed within culture bacteria.<sup>79</sup>

#### **Models predicting resistance rates in localised clinical environments**

Lipstitch and Bergstrom<sup>80</sup> and Seville and colleagues<sup>81</sup> produced models of the rates of antibiotic resistance within an intensive care unit (ICU) to investigate the impact of local control measures. The model was used to investigate the effect of various factors, such as transmission rates within the hospital, length of stay, antimicrobial policy and handwashing policies use on the persistence of resistance in the unit. These models focused on the rates observed within the unit and did not predict changes in the rates observed within the wider community resulting from changes in practice.

### **Models treating the rate of resistance as an exogenous variable**

Khan and colleagues<sup>82</sup> developed a decision model of the management of latent tuberculosis infection which identified the optimum intervention for a range of geographical regions conditional upon the rate of drug resistance observed in each region. Goodman and colleagues<sup>68</sup> developed a decision model to identify the optimum first line drug as a function of time for malaria treatment conditional on different assumptions regarding the development of drug resistance over time. The model was conditional on assumptions regarding the relationship between the decision to adopt a therapy and the subsequent rate of development of resistance to that therapy. Although these models did address the impact of changes in resistance between geographic regions or over time, they treated the rate of resistance essentially as exogenous variables and did not directly model the relationship between the therapeutic decisions and the subsequent rates of development of resistance.

### **Empirical studies of the rate of development of resistance**

Mahamat and colleagues<sup>83</sup> and Lopez-Lozano and colleagues<sup>84</sup> used ARIMA time series models to examine the empirical relationship between the uses of fluoroquinolone and resistance amongst *Escherichia coli* urinary tract isolates and between the use of both ceftazidime and Gram-negative bacilli and imipenem and *Pseudomonas aeruginosa*, respectively.

### **Summary**

No models were identified which would prospectively predict the change in rate of development of resistance in the global clinical population arising from a change in therapeutic practice. This is perhaps not surprising considering the complexity of and uncertainty surrounding potential interactions between geographic and therapeutic patient populations, the mechanism and dynamics of the development of antibiotic resistance and the potential for cross-resistance and the potential interactions between bacterial populations arising from the exchange of genetic material (*Figure 14*).

Predictive models of resistance in a local population have been developed and more global decision models commonly condition on estimates of the rate of resistance. Empirical models are available to evaluate retrospectively the impact of a change in therapeutic practice on the development of resistance.

## **A conceptual framework for the economic evaluation of policies against MRSA**

### **Introduction**

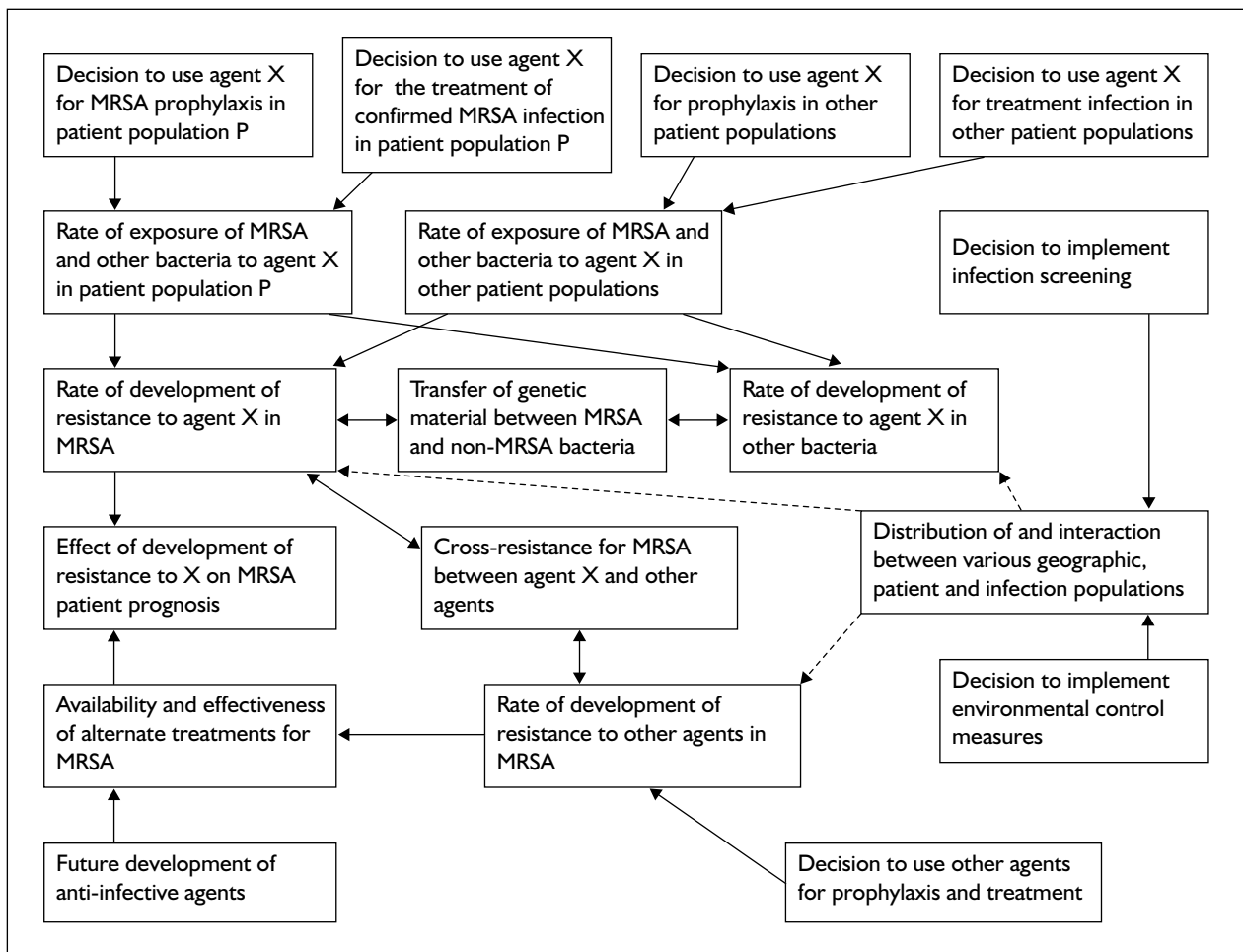
Although this report focuses on a very specific question – the cost-effectiveness of glycopeptides as prophylaxis against MRSA in high-risk surgical patients – the issue of drug resistance potentially broadens the evaluative questions markedly. This section considers the complexities associated with evaluating policy options for controlling MRSA (indeed, managing any disease where resistance is an issue). Informed by this, it also describes what an ideal evaluative framework might be for these sorts of policy options. Although the cost-effectiveness analysis reported above is based on a very specific part of this framework, it is important to recognise the other elements of a full evaluation that are not explicitly considered in this ‘partial’ analysis. Although not a formal systematic review, this section is informed by a formal literature search using the strategy defined in Appendix 1.

The next section considers different dimensions of the evaluation problem regarding MRSA and, for each, what method might be used to deal with these complexities. A third section assesses the basis on which simplifications might be made to an evaluation such that it might be tractable analytically but of value to guide decision-making.

### **Dimensions of complexity in evaluating policies for MRSA control**

#### **The interdependence of decisions**

In most areas of health technology assessment, it is possible to isolate the decision problem being addressed from others. For example, in considering the cost-effectiveness of a new cholesterol-lowering therapy for primary prevention of heart disease, the use of the therapy is unlikely to influence the effectiveness or cost of other interventions. This is still a simplification in that the cost-effectiveness of an intervention which extends life sufficiently for enough patients to receive the new cholesterol-lowering therapy may hinge on the latter’s cost-effectiveness. In other words, the new cholesterol-lowering therapy may extend an individual’s life sufficiently to make saving their life with an apparently independent intervention cost-effective. However, these may be considered weak interdependencies which can safely be assumed away because policy decisions are unlikely to be sensitive to whether or not they are included.



**FIGURE 14** Potential interactions in a global model of the development of antimicrobial resistance consequences

In the case of managing diseases with therapies where resistance is an issue, the assumption of interdependence is stronger. This is illustrated in *Figure 14*, which shows the relationship between different types of decision and clinical effects in the context of the use of a given antibiotic. The interrelated decisions include whether to use the antibiotic as a prophylactic in one specific patient population, whether to use it as a prophylactic in one or more other patient populations, whether to use it as a treatment (of clinical infections) in a specific patient population, whether to use it as a treatment in one or more other patient populations and whether to use other MRSA control strategies (e.g. MRSA screening or environmental controls).

Typically, the decisions (at least to the extent to which they apply to different patient populations) would be considered independent. However, *Figure 14* shows that this assumption may be unsafe to the extent that the decisions interact through the rate of exposure (in different patient

populations) of MRSA to one or more agents and the rate of development of MRSA resistance to one or more agents. In short, the cost-effectiveness of a range of policy options available for one patient group (e.g. whether to give a particular antibiotic to patients undergoing hip replacement in one hospital) may influence the cost-effectiveness of policy options for another patient group [e.g. whether to use that antibiotic (or, because of cross-resistance, another) in patients having heart surgery in another hospital].

How can an evaluative framework be developed to reflect this interdependence? In principle, this can be dealt with as an extension to standard decision modelling by linking the range of decisions. Thus such a model would, in effect, be simultaneously informing a cluster of decisions – that is, because of interdependence, it would make little sense to make decisions one at a time, and they should be addressed at the same time. Such **decision** models would make use of the **epidemiological** models that have been developed to model resistance (see

the section ‘Use of epidemiological and decision analytic techniques to model antibiotic resistance’, p. 55), but also include appropriate parameters for economic analysis such as cost, utilities and prognosis. Although, given time and funding, such models could be developed, they would have to overcome two important challenges. The first is the difficulty of forecasting how drug resistance will develop over time, given its variability and the limited evidence base. This is a specific example of a general modelling problem of handling (often extreme) uncertainty in decision models in terms of parameter estimates. Although there is no ‘magic bullet’ to overcoming uncertainty, recent methods developments have provided a framework to quantify uncertainty in parameters,<sup>85</sup> express this in terms of decision uncertainty<sup>86</sup> and assess the implications for research priorities and design.<sup>87,88</sup>

The second challenge is the need to decide where the boundaries would be drawn. That is, which decisions would formally be included in the model given that, in theory, there are numerous interdependencies. As for the example of the cholesterol-lowering therapy in the ‘standard economic analysis’ described above, a judgement would have to be taken as to when the strength of the interdependency is sufficiently weak to leave out of the model under the assumption that its inclusion is unlikely to change the results.

### **Large range of possible policy options**

In the face of antimicrobial drug resistance, there is a large range of possible policy options. This was emphasised by Coast and Smith, who identified 27 groups of policy options to contain antimicrobial resistance.<sup>89</sup> These are summarised in *Table 13*. In principle, these policy options could be used individually or in combination. In terms of economic evaluation, they could be considered to be relevant comparators (individually or in combination) to each other and should be assessed in the same model. This would pose a number of challenges. As for modelling resistance, the first would be the uncertainty in the input parameters. In particular, there is likely to be limited and poor quality trial data comparing the different options. As described earlier, decision theory and value of information methods provide a potential way through this. A second, and related, problem is the lack of head-to-head trial data comparing all the policy options. This is not unusual in many technology assessment activities, and methods of indirect and mixed treatment comparisons exist to synthesise data in the absence of head-to-head trials.<sup>90</sup>

Despite the availability of these methods, however, the simultaneous comparison of all these policy options remains a major task. Some degree of prioritisation would seem appropriate – for example, some of the policy options may simply not be relevant for some local health systems. It would, of course, be necessary for this work to be adequately resourced and given a realistic timetable.

### **Infectious disease**

The problem of resistance is a major source of added complexity in considering appropriate patient management regarding MRSA. However, the evaluation of policy options in the context of infection which can spread from one individual to another represents another level of complexity, and this clearly applies to MRSA, although the spread of the infection is typically in its preclinical stage. The implication of infection is that it is not necessarily reliable to assume that the rate of infection amongst a susceptible population is fixed as would typically be the case in decision models. In reality, the rate of infection is a function of the number of infected individuals in the community and should also include individual level characteristics (e.g. whether or not the individual is immune-compromised) and context level characteristics (e.g. the rate of infection within the hospital or the unit where the individual is located). Alongside this, consideration of the risk of carriage and the uncertainty of the relationship between carriage and infection is relevant. This increases the challenges associated with capturing the consequences of a change in the resistance rate. However, it is possible to adapt decision models to make them ‘dynamic’. That is, they explicitly allow for the effects of herd immunity in a way that cannot be achieved with a static model.<sup>91</sup> Such models have been used for the economic evaluation of interventions to control infectious diseases, such as vaccination [which is an option in the context of MRSA (see *Table 13*)].<sup>92</sup> A key issue to consider is the extent to which failing to reflect the dynamic nature of a disease process in a decision model will lead to potentially misleading results and policy guidance.

### **Cross-sectoral and macro economic effects**

Another feature of the evaluation of MRSA control activities is the fact that the costs and effects of alternative options will often extend outside the healthcare sector. This ‘inter-sectoral’ impact is a feature of the evaluation of many public health programmes and interventions. For example, in evaluating interventions for individuals with illegal drug dependence, there are likely to be effects



**TABLE 13** Policy strategies for containing antimicrobial resistance<sup>89</sup>

<p><b>Strategies for containing the emergence of resistance</b></p> <p><b>By optimal use</b>            Antimicrobial cycling            Removal of potential septic foci/prostheses            Choosing the optimal agent, dose and dosage frequency            Use of drug combinations</p> <p><b>By reducing use through the use of alternative treatments</b>            Use of antiseptics            Use of cranberry juice for urinary tract infection            Using probiotics</p> <p><b>By reducing use through provision of improved immunity</b>            Increased vaccination            Improving nutrition            Minimise time patient immunocompromised</p> <p><b>By reducing use without providing an alternative treatment</b>            Education of professionals            Patient education            Rapid diagnosis            Control of sensitivity data related to prescribers            Antimicrobial policies            Restriction of drug availability            Regulation of the use of antimicrobials in agriculture            Financial incentives</p>
<p><b>Strategies for containing the transmission of resistance</b></p> <p><b>By early recognition of resistance</b>            More rapid diagnostic techniques            Screening of patients/staff            Surveillance</p> <p><b>By reducing infectivity</b>            Use of antimicrobials to reduce infectivity</p> <p><b>By reducing transmission possibilities</b>            Isolation            Handwashing            Improvements in bed spacing</p> <p><b>By reducing susceptibility to infection</b>            Improve immunity by vaccination to reduce susceptibility            Improve nutrition</p>

(resource and other) on other public sector activities, most notably criminal justice. In the case of MRSA infection (and antibiotic resistance more generally), there are potentially extensive macro-economic effects.<sup>93</sup> At a domestic level, this would involve the adverse health effects of infection and resistance (from MRSA, but also susceptibility to other infections) leading to reduced productivity at work, which, other things being equal, would reduce national output and income. In turn, this

would lead to reduced national savings, and hence investment, as well as welfare. In terms of production, lower productivity can lead to a reduction in company profits and hence in investment and employment. Increasing unemployment, together with lower profits and output, can reduce government revenues and increase government transfers; this can lead to reductions in health expenditure. Overall, there will be a reduction in societal welfare that, in principle, can extend much further than just health. At the broadest level, the problems of infection and resistance can have international implications in that, through individuals travelling abroad, drug resistance can spread.<sup>94</sup>

Although much depends on the extent of MRSA and other forms of antimicrobial resistance, the standard economic evaluation may be very limited in informing decisions about policy options. This is because these studies typically focus on costs to the health sector and changes in health outcomes within a given jurisdiction. However, these macro-economic effects, if they are strong enough, can have a wider set of resource and welfare effects beyond national boundaries. Furthermore, there is a dynamic effect of such ‘health shocks’: an initial health effect has knock-on effects across different sectors and over time. It should be said that these macro-economic effects are potentially important for a range of diseases – for example, the economy-wide effects of HIV in many African countries is well known, and there is concern about the effects of a pandemic in avian influenza.

Part of the reaction to these macro-effects is in terms of the policy options to be evaluated. At a domestic level, policy options may not be confined to the healthcare sector and could include wider industrial policies or government expenditure and taxation decisions. The international dimension in how the effects spread means that some degree of coordinated global policy response might be appropriate.<sup>89</sup> How can evaluation methods be extended to reflect these wider effects?

There has been some consideration of the use of general equilibrium models for policy evaluation in this context.<sup>93</sup> These are models, similar to those used by the Treasury and other economic forecasters, which explicitly quantify the economic knock-on effects of health shocks. For example, Smith and colleagues describe a “computable general equilibrium (CGE) model”. It is based on an economy made up of a set of economic agents – consumers, producers and government.<sup>93</sup> Each of these is assumed to have a maximand and to

make various decisions to satisfy this maximand subject to constraints. For example, a consumer is assumed to maximise their utility by allocating their time to paid employment and using income to purchase commodities. The interaction of these economic agents – each maximising their maximand subject to the relevant constraints – can result in an equilibrium when a set of prices are reached at which the level of production and consumption within each sector results in the quantity of supplied goods equalling the quantity demanded across all sectors. The macro effects of resistance are modelled as an external shock to the system, and policy options assessed by how the shock affects the macro economy. By assessing the new (post-shock) equilibrium in each sector, it is possible to estimate the net costs and benefits of each policy. In Smith and colleagues' CGE model, changes in national income from alternative policies are estimated and the distribution of those changes across different groups, and also levels of production and employment. Measures of welfare (such as Hicksian compensating variation) can be used, within a cost–benefit analysis framework, to assess the efficiency of alternative policy options. Smith and colleagues' model estimates that MRSA of 40% in the UK would lead to a reduction in gross domestic product (GDP) of between 0.4 and 1.6% (£3–11 billion), or about 6–20% of NHS expenditures in 1995.<sup>93</sup>

### Modelling the future

It can be seen that assessing the cost-effectiveness of programmes and interventions in the context of resistance involves modelling under considerable uncertainty. One aspect of this uncertainty relates to modelling the future. There are several aspects of this. The first relates to the fact that the potential for drug resistance can result in policies which improve the health of current patients actually having a negative health effect on future patients. In the context of prophylactic antibiotics in surgical patients for MRSA, one of the factors referred to previously about the interdependence of decisions is the fact that the use of an antibiotic (such as the glycopeptides) as a form of prophylaxis **today** may lead to an increase in resistance to that drug, which, in turn, may reduce the available treatments for patients with clinical infections **in the future**. In other words, today's health gains are at the expense of tomorrow's health decrements – this could be characterised as a form of an inter-generational distribution problem.

Standard economic evaluation methods can deal with the fact that some patients gain and some lose from a particular policy decision. This is

achieved by simply estimating a net health effect (gainers minus losers) across patients. An example of this is the evaluation of therapies which are efficacious in some patients but have side-effects in others and it is not possible to distinguish these patients when the treatment decision is made. In such a situation, the health benefit of the intervention is an average of the health gain and the health reduction weighted by the proportions of patients who experience these two types of outcomes. However, this standard approach to deal with 'gainers' and 'losers' is used when these two types of individual are contemporaneous. The MRSA and resistance problem is that the gainers are likely to be today and the losers are likely to be future generations of patients needing an effective treatment for MRSA.

Although not standard in economic evaluation, this feature could be handled by aggregating costs and benefits across time. Instead of modelling the costs and benefits of a therapy in a cohort of patients today, the model could model an evolving cohort over time, which would include those future patients needing treatment for MRSA infection. This is analogous to some screening models where a prevalence cohort of individuals is augmented by incidence cases over times. It also has parallels with the dynamic infections models referred to in the previous section. An important methodological issue with such a model, however, relates to the role of discounting. This is conventional in economic evaluations to reflect positive time preference which is anticipated in individuals and society – that is, the desire to bring forward benefits and to delay disbenefits.<sup>34</sup> The use of an evolving cohort in a model with conventional discounting would, therefore, reduce the estimated health decrements for future patients (requiring treatment) compared with the health benefits for current patients (requiring prophylaxis), which may be considered inappropriate.

A related issue concerns the fact that the decision about whether to use antibiotics such as glycopeptides for prophylaxis is characterised by 'irreversibilities'. That is, once the decision to use the drug in this way is made, on the basis of what is currently known, it may be impossible to reverse the decision. This is because the greater exposure of the population to the drug is likely to increase drug-resistant strains of the bacteria, and this is unlikely to be reversed. This situation contrasts with decisions about other therapies where, if more evidence emerges about the effects and costs of a therapy, a past decision can be reversed, albeit

at some cost. The fact that a decision may be irreversible (or only reversible at high cost) has implications for how that decision is made. Methods have been suggested about how to reflect 'irreversibilities' in economic evaluation. These include option pricing methods which, using approaches developed in financial economics, seek to model the emergence of future evidence and estimate the costs and benefits of delaying decisions.<sup>95</sup> These methods have not been used in applied economic evaluations in healthcare and require further work to make them appropriate to the type of decisions facing health system decision-makers.

Another feature of modelling the cost-effectiveness of management options related to MRSA is that the costs and benefits associated with current decisions are likely to rest crucially on the future development of health technologies. Perhaps the most obvious example is that the anticipated future costs and health disbenefits resulting from antibiotic resistance are likely to be less as new antibiotics are developed because resistance will not necessarily reduce treatment options over the longer term. However, reflecting these possible future developments in economic evaluations is difficult. Again, this is due to the marked uncertainty associated with forecasting the future.

## Conclusions

This chapter has provided a review of literature relevant to the economic evaluation of glycopeptides in prophylaxis. A series of reviews have been undertaken that relate to applied studies of glycopeptides specifically, of other forms of prophylaxis, in MRSA and in areas where resistance is a problem. Reviews have also been presented of epidemiological modelling work relating to resistance, and conceptual issues in economic evaluation in which resistance is an issue. From these reviews, it is possible to draw several conclusions:

- Published economic evaluations of glycopeptides do not address the decision problem facing the NHS. None has been undertaken in the UK, no study compared the full range of clinical options and most studies

used condition-specific measures of effect rather than the generic measures of health which are essential for system-level decision making (e.g. QALYs).

- Across the various reviews, few insights were provided on how to assess cost-effectiveness in the context of resistance. No studies modelled cost-effectiveness alongside epidemiological models of resistance. Those studies that considered resistance at all in a quantitative manner did so using sensitivity analysis or as a component of treatment failure, and few studies used empirical estimates of resistance.
- In a number of important respects, the economic evaluation of interventions in the areas where drug resistance is an issue is characterised by complexity. Although by no means unique compared to other disease areas, few others have the same number of complexities. In particular, the infectious nature of the disease, the interdependences of decisions and the extreme uncertainty about the future are major challenges for any evaluation.
- There are methods available which could begin to address these complexities. Some of these methods have been used before in economic evaluation – for example, the use of Bayesian statistical methods and value of information methods to be explicit about uncertainties and use these to prioritise future research. Other approaches have not been used very widely in the health field and would need further development – for example, macro-economic modelling. It is clear, however, that a major programme of research would be necessary to develop and apply these methods to the management of MRSA in the UK.
- In addition to estimating the cost-effectiveness of glycopeptide prophylaxis with regard to the costs and effects for the individual who may receive prophylaxis, it is also necessary to consider the potential for an increase in the rate of development of antibiotic resistance and its consequences across the future patient populations. Also, as it is likely that the effect of glycopeptide prophylaxis on antibiotic resistance will depend on the extent of usage, there is a need to consider the potential implementation across the patient population rather than simply considering the cost-effectiveness for individuals.



# Chapter 6

## Economic model

### Introduction

In order to investigate whether there is a threshold level of MRSA prevalence at which it is cost-effective to switch from non-glycopeptide to glycopeptide antibiotic prophylaxis in surgical environments with a high risk of MRSA infection, the aim was to develop a new decision analytic model. There are a number of reasons why the modelling work presented in this chapter should be seen as **indicative** rather than **definitive**. The first of these is the number of major complexities associated with the economic evaluation of options in the field of MRSA (see the section 'A conceptual framework for the economic evaluation of policies against MRSA', p. 56). Second, the review of the economic evaluation evidence in Chapter 4 did not reveal any head-to-head studies which directly compared the prophylactic use of vancomycin and teicoplanin against all relevant non-glycopeptide prophylaxis comparators for use in surgery. No studies which evaluated glycopeptide prophylaxis were undertaken in the UK, and infection control practices and SSIs are likely to differ substantially across settings. The supplementary literature reviews (see the sections 'Economic evaluations of antibiotics where antibiotic resistance is a problem', p. 46 and 'Use of epidemiological and decision analytic techniques to model antibiotic resistance', p. 55) provided few insights of how to assess cost-effectiveness of antibiotics in the context of resistance.

In addition, the results of the clinical review in Chapter 3 have highlighted the major limitations of the clinical evidence. In particular, only two studies reported the number of SSIs caused by MRSA.<sup>16,17</sup> This dearth of data on the **effectiveness** of glycopeptides in the prophylaxis setting represents a major limitation in what is possible in terms of estimating their **cost-effectiveness**.

It has therefore not been possible to reflect the range of complexities in MRSA modelling within the time available for the current analysis. Although methods are available that could begin to address these complexities, some of them have not been widely used in the health field and a major programme of research would be necessary

to develop and apply these methods to the management of MRSA in the UK. Despite these difficulties, it is hoped that the indicative modelling presented in this chapter provides a contribution to decision making in this field. In particular, it describes a modelling approach that could be used more fully as stronger clinical data emerge. The model has been developed to estimate costs from the perspective of the UK NHS and Personal Social Services (PSS) and health outcomes in terms of QALYs and was developed in Excel.

### Exemplar: hip arthroplasty

Based on the effectiveness and cost-effectiveness reviews, it is clear that resource use, costs and outcomes associated with antibiotic prophylaxis differ by type of surgery. Hence it was decided to focus on a single area of surgery, by way of an exemplar, for the indicative economic model. The surgical speciality chosen was hip arthroplasty for the following reasons:

1. Hip arthroplasty is classed as a 'clean' surgical procedure, that is, the operative wound is not likely to be infected or inflamed with pre-existing infections and is closed.<sup>96</sup>
2. This group of patients is relatively homogeneous.
3. The group is at substantial risk of serious SSI including a high risk of MRSA infections.
4. Data availability is, in principle, greater in this type of surgery compared with others because of the high volume of orthopaedic surgery undertaken.

The use of surgical antibiotic prophylaxis is only recommended in procedures where there is a high risk of infection, such as colorectal surgery, or where the consequences of infection can be severe, such as joint arthroplasty. There is a general consensus that the minimum number and doses of antibiotics need to be administered in such a way as to provide sufficient cover during surgery, while at the same time prescribed appropriately to minimise the development of antimicrobial-resistant bacteria. SSIs after hip arthroplasty result from a variety of factors, including bacterial contamination of the wound during the procedure, virulence of the contaminating organisms, factors

within the surgical wound and patient risk factors such as concomitant disease. Use of prophylactic antibiotics is generally recommended after hip arthroplasty to minimise SSIs.<sup>97</sup> A dose of an appropriate antibiotic is usually administered within 60 minutes of the surgical incision to ensure that adequate drug concentrations are present in the serum, tissue and wound during the entire time that the incision is open and at risk of bacterial contamination. Prophylactic antimicrobials should then be discontinued within 24 hours after completion of the procedure.

## Methods

### Purpose

The purpose of the indicative modelling is to provide a framework within which the cost-effectiveness of prophylactic interventions for high-risk surgery can be assessed. Using available evidence and clinically informed assumptions, the model seeks to illustrate how the threshold baseline risk of clinical MRSA infection at which the use of glycopeptides becomes cost-effective might be estimated. The analysis assessed the relative cost-effectiveness of vancomycin, cephalosporin or their combination.

Given the complexities and lack of data, as explained previously, a number of assumptions and simplifications are made in the analysis. Perhaps the most important of these is that long-term resistance to glycopeptides has not been explicitly modelled. It should be reiterated, therefore, that this analysis seeks to indicate how a model might be developed to estimate a threshold baseline risk; its results are of limited direct policy relevance.

### Model structure

A decision model was developed to estimate the expected costs, the expected effects in terms of QALYs and the expected glycopeptide usage for patients receiving vancomycin, cephalosporin or vancomycin and cephalosporin used in combination. The decision model is illustrated in *Figure 15*. For each treatment arm the probability of no infection, MRSA infection and non-MRSA infection was estimated. For the two types of infection arms, the probability of a deep or superficial infection was estimated; this was assumed to be independent of whether it was an MRSA or non-MRSA infection. These rates were conditional on the 'baseline' MRSA infection rate with cephalosporin prophylaxis and non-MRSA infection rate with cephalosporin prophylaxis.

The odds ratios (ORs) for MRSA and non-MRSA infections for vancomycin prophylaxis compared with cephalosporin were estimated from a randomised trial. The baseline infection rates for cephalosporin prophylaxis were converted to odds. These were multiplied by the relevant ORs and converted back to probabilities to estimate the infection rates for vancomycin prophylaxis.

The baseline infection probabilities were converted into odds and multiplied by the relevant ORs for the prophylaxis options compared with cephalosporin prophylaxis.

For the no infection, deep and superficial infection populations, the risk of death was estimated; this was assumed to be independent of MRSA or non-MRSA infection. Costs were estimated for cephalosporin or vancomycin and cephalosporin prophylaxis and treatment for non-infected, deep and superficial MRSA and deep and superficial non-MRSA patients. QALYs were estimated for non-infected living patients and a utility decrement was incorporated for patients with deep and superficial infections. The utility decrement was estimated by multiplying the mean hospital stay by a utility decrement. In addition, the number of days of glycopeptide treatment for patients with deep and superficial MRSA infections was estimated.

### Parameters for use in the model

The parameters in the model can be divided into the following categories:

- baseline infection rates: SSI rates; MRSA SSI rates
- effectiveness estimates for interventions in terms of the relative reduction in infection rates
- consequences of infection: impact on survival, length of hospital stay, health-related quality of life (HRQoL) and treatment intensity.

### Clinical effectiveness: which infection rates should be used?

The model aims to identify the baseline MRSA SSI rate in a surgical patient cohort that would justify the use of prophylactic glycopeptide antibiotics, rather than non-glycopeptide antibiotics. As such, baseline surgical site MRSA infection rate is an output of the model rather than an input. However, to provide some context for these threshold estimates, it would be helpful to present some UK statistics on these risks. Nationally obtained infection control surveillance data report MRSA bacteraemia incidence rates in both medical and surgical hospital admissions.<sup>98</sup>

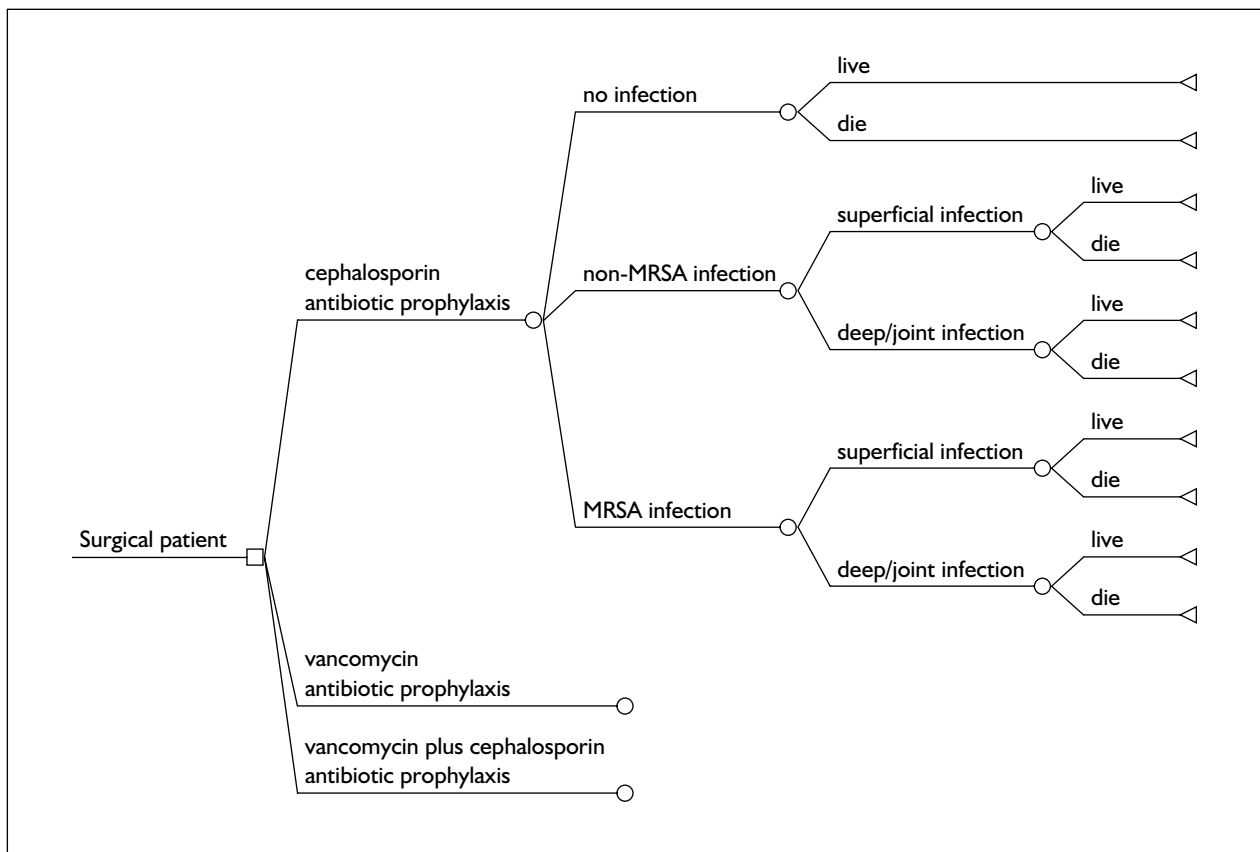


FIGURE 15 Model diagram

However, the link between bacteraemia rates and SSI rates is not well understood and, therefore, it is not appropriate to apply the infection control surveillance data that use MRSA bacteraemia incidence rates within our model.

The Surgical Site Infection Surveillance Service (SSISS), formerly known as the National Nosocomial Infection Surveillance Service (NNIS), was established by the Department of Health and the Health Protection Agency in 1996.<sup>99</sup> Using CDC definitions for infections (Table 14), this service provides information from 102 hospitals in England, reported by surgical procedure, and provides information on causative organism, severity of infection and length of hospital stay.<sup>100</sup> The results from this study reflect considerable variation between hospital SSI rates and the need for individual hospitals to be aware of their local SSI rates for application to our model. These data would make the model's estimate of a threshold relevant to local decision-makers because individual hospitals have information on their SSI rates. Therefore, they will be able to determine whether their MRSA infection risk is above or below thresholds derived in the model at which glycopeptides are potentially cost-effective.

SSISS figures from a survey of 102 English hospitals suggested that 363/16291 (2.23%, 95% CI 2.0 to 2.5%) primary total hip arthroplasties resulted in SSI. Of these, 294 (1.80%) were superficial wound infections, 38 (0.23%) were deep wound infections and 30 (0.18%) were joint infections.<sup>99</sup> MRSA appears to be the most common pathogen to cause early SSI in hip arthroplasty;<sup>99</sup> 24.3% were positive for MRSA, 21.9% for MSSA and 15.3% for CNS.

Coagulase-negative *Staphylococcus* sp. may be more important in deep infections involving the joint that ultimately lead to late joint failure. MRSA may play a limited role in late hip arthroplasty failure.<sup>101</sup> Therefore, the use of glycopeptide or non-glycopeptide antibiotics around surgery is not likely to have an effect on late infective failure. As a result, the primary analysis reported here examines the impact of a change in antibiotic policy on the incidence of early SSIs only.

### Baseline MRSA SSI rates

In our model, the baseline incidence of SSI due to MRSA was 1.2% in the base case, with a plausible range of 0–0.3% from Zanetti and colleagues; however, this related to CABG, not orthopaedic

**TABLE 14** Infection definitions used in the SSISS database<sup>100</sup>

Type of infection	Definitions
Superficial incisional	Occurs within 30 days of surgery. Involves only skin and subcutaneous tissue and meets at least one of the following criteria: 1. Purulent drainage from superficial incision. 2. Organisms are grown and pus cells seen from aseptically obtained swab/tissue from the superficial incision. 3. At least two of the following signs and symptoms: (a) pain or tenderness, localised swelling, redness or heat, and (b) (i) the clinician diagnoses an infection or (ii) the superficial incision is deliberately opened by a surgeon to manage the infection, unless the incision is culture-negative.
Deep incisional	Occurs within 30 days (no implant) or 1 year (implant) of surgery. Involves deep fascia and muscle layers. Appears to be related to the procedure and meets at least one of the following criteria: 1. Purulent drainage from the deep tissue but not the joint or bone. 2. Organisms are grown and pus cells seen from aseptically obtained swab/tissue from the deep incision. 3. A deep incision which spontaneously dehisces or is opened by the surgeon when the patient has fever (>38°C), localised pain or tenderness unless the incision is culture-negative. 4. An abscess or other evidence of deep infection found during re-operation, or by histopathological or radiological examination.
Joint/bone infection	Occurs within 30 days (no implant) or 1 year (implant) of surgery. Involves joint and/or bone related to the site of the operation with any other tissues. Appears to be related to the procedure and meets at least one of the following criteria: 1. Purulent drainage from a drain which is placed through a stab incision into the joint. 2. Organisms are grown and pus cells seen from aseptically obtained swab/tissue from the joint/bone. 3. An abscess or other evidence of joint/bone infection found during re-operation, or by histopathological or radiological examination. 4. The patient has at least two of the following signs or symptoms with no other recognised cause: joint pain, swelling, tenderness, heat, evidence of effusion or limitation of movement and at least one of the following: (a) organisms and white blood cells seen on Gram stain of the joint (b) positive antigen test on blood, urine or joint fluid (c) cellular profile and chemistry of joint fluid compatible with infection and not explained by an underlying rheumatological disorder (d) radiological evidence of infection, e.g. abnormal findings on radiographs, CT scans, MRI, radiolabelled scan (gallium, technetium, etc.).
CT, computed tomography; MRI, magnetic resonance imaging.	

surgery.<sup>37</sup> The purpose of the model was to identify the threshold value, within this range, at which glycopeptides might be considered cost-effective.

### Treatment effect

The treatment effect of vancomycin was applied to this baseline rate. This assumes that standard practice in the UK is to use a non-glycopeptide for antibiotic prophylaxis in primary hip arthroplasty, as currently recommended by the British Orthopaedic Association.<sup>97</sup>

The effectiveness review reported in Chapter 3 shows how few data are available on the effect of glycopeptides specifically on MRSA SSIs, and that

no orthopaedic surgical trials reported MRSA rates. The treatment effect used was, therefore, derived from the wider set of effectiveness data from other clean surgery trials to this baseline MRSA rate.

Of the SSIs that occur after primary hip arthroplasty, 80.7% are superficial wound infections, 10.3% are deep wound infections and 8.1% are joint infections.<sup>2</sup> In the model, it is assumed that the three categories of SSIs occur with this relative frequency in all treatment arms. It was assumed that the treatment effect of glycopeptides was equal across all categories of SSIs. Finally, it is assumed that 24.3% SSIs are MRSA, equally across all categories of SSIs.<sup>99</sup>



## Consequences of infection

The consequences of infection can be divided into (1) impact on survival, (2) length of hospital stay, (3) HRQoL and (4) treatment intensity.

### Mortality attributable to infection

From the trials included in the effectiveness review, it was not possible to determine mortality attributable to infection as these studies were small to estimate the risk of such a rare event.

Data on mortality attributable to SSI in general, based on Ridgeway and colleagues' SSISS study,<sup>99</sup> were analysed, with mortality for hip arthroplasty patients with SSIs being adjusted for confounders [age, sex, American Society of Anesthesiology (ASA) class, wound class, elective/emergency surgery, duration of operation, complexity of operation, trauma, time in hospital to operation].<sup>2</sup> Mortality without an SSI was 2.4%, versus 7.4% with SSI (adjusted OR 1.8, 95% CI 1.3 to 2.7;  $p < 0.002$ ). Mortality for superficial SSI was 5.7%, and for deep/joint SSI it was 11.9%.

Mortality attributable to MRSA SSI was not reported in Coello and colleagues' SSISS study.<sup>2,99</sup> MRSA infection does not appear to lead consistently to increased mortality over other types of infection. The underlying comorbidity of patients who develop MRSA infections appears to confound and exaggerate the effect of MRSA.<sup>102</sup> In our model, it is assumed that MRSA infections have the same attributable mortality as other infections.

### Length of hospital stay attributable to infection

SSI is likely to increase length of hospital stay (LOS), due to the interval from detection, through treatment and infection resolution to discharge. From the trials included in the effectiveness review, it was not possible to determine LOS attributable to infection.

From SSISS data, the median time to detection of SSI was 8 days for superficial incisional, 11 days for deep incisional and 11 days for joint/bone infections. For each procedure, the mean length of stay doubled for patients with SSI.<sup>99</sup> The median LOS was 9 days for primary total hip arthroplasty patients without SSI and 17 days for patients with SSI. These LOSs have not been corrected for confounding factors and means (necessary for the decision model) were not reported. However, these data were analysed further and increased LOSs for hip arthroplasty patients with SSIs were adjusted for confounders (i.e. age, sex, ASA class, wound class, elective/emergency, duration of operation, complexity of operation, trauma, time in hospital

to operation).<sup>2</sup> The geometric mean LOS for hip arthroplasty patients without SSI was 11.1 days. The mean extra LOS attributable to all SSIs, identified through multivariate analysis, was 11.5 days (95% CI 10.3 to 12.8 days). The mean extra LOS attributable to superficial SSI was 8.9 days (95% CI 7.7 to 10.2 days). The mean extra LOS attributable to deep/joint SSI was 22.8 days (95% CI 19.2 to 26.9 days).

The presence or absence of an increased LOS due to MRSA over other infections was not reported in the SSISS studies.<sup>2,99</sup> Increased LOS has been reported for MRSA bacteraemia compared with MSSA (9 versus 7 days,  $p = 0.045$ ).<sup>103</sup> In this study, after correcting for confounders, the authors report a median attributable length of stay of 2 days. It is not clear whether these data, from a 1997–2000 US cohort of bacteraemia patients, are applicable to hip arthroplasty-associated SSI. In a model of the cost-effectiveness of different MRSA screening methods, Kunori and colleagues added a range of number of days LOS to account for MRSA screening delays.<sup>104</sup> However, when treating an SSI, cultures would be taken whether the infection was MRSA or not, so there would be no incremental difference. In the absence of compelling evidence to the contrary, it is assumed that there is no increased LOS due to MRSA over other infections.

### Quality of life, utility data and QALYs

As noted in the review of economic evaluations of glycopeptides, only one study included a generic measure of health, based on QALYs.<sup>37</sup> However, it was not possible to use these QoL weights since they were direct valuations of health states specific to cardiothoracic surgery. One study did use a generic outcome measure [Short Form with 36 Items (SF-36)] in orthopaedic surgery in order to assess the impact of SSIs 1 year after their initial detection, post-orthopaedic surgery.<sup>105</sup> The study was based on a pairwise, matched control within cohort study. All patients had undergone orthopaedic surgery and the case patients had an SSI postoperatively whereas the control patients were free of SSIs. It was found that case patients experienced substantial reductions in their HRQoL 1 year post-SSI detection compared with the control patients, with the largest decrements in their HRQoL observed in the physical functioning and role-physical domains. It is possible to generate utility scores based on the SF-36 scores; however, to do so would have required access to individual patient data and the authors of the study did not respond to requests for access to these data.

Tengs and Wallace have identified 1000 HRQoL estimates based on a review of the literature and found a utility weight for an infection relating to an artificial joint of 0.9.<sup>106</sup> Therefore, infection was related to a 0.1 decrement in utility. In order to convert these data into QALYs, four elements were combined:

1. A utility decrement associated with infection of 0.1 was calculated, based on Tengs and Wallace's data.<sup>106</sup>
2. The mortality associated with infection (as described in the section 'Mortality attributable to infection', p. 67) from which the probability of dying with no infection, a superficial infection and a deep/joint infection were calculated.<sup>2</sup>
3. Life expectancy [based on life-tables for 65-year-old men in the UK based on data for 2002–2004 ([http://www.gad.gov.uk/Life\\_Tables/Interim\\_life\\_tables.htm](http://www.gad.gov.uk/Life_Tables/Interim_life_tables.htm))].
4. The national QoL norms by age and sex (0.78 for 65–74-year-olds and 0.73 for ≥75-year-olds) (<http://www.york.ac.uk/inst/che/pdf/DP172.pdf>).

QALYs (and costs) were discounted at 3.5% per year. Patients who survived an infection experienced 8.74 discounted QALYs over a lifetime (based on males aged 65 years).

#### **Infection-related interventions and treatment intensity**

Of the SSIs that occur after primary hip arthroplasty, most are superficial wound infections, with only 18.4% being deep wound or joint infections.<sup>99</sup> Superficial infections are likely to require less intensive intervention than deep or joint infections. Interventions following infection can be minor, such as antibiotics, or there can be a more major requirement for surgical intervention, either for debridement of the wound or for revision arthroplasty.<sup>107</sup> In a study of a cohort in Avon, early infection after primary hip arthroplasty occurred in 14 out of 1567 procedures, and eight were treated with antibiotics, two had exploration, debridement and

washout and four had exploration, debridement and washout, and a revision procedure.<sup>107</sup>

Based on this study and clinical advice, it is assumed that the following level of intervention occurs for each severity of SSI:

- superficial SSI: antibiotic treatment
- deep/joint SSI: exploration, debridement and washout, antibiotic treatment.

There are a number of antibiotics used for treatment of non-MRSA infections. For the purpose of this particular exemplar, we have assumed treatment with oral erythromycin (Kay P, Consultant Orthopaedic Surgeon: personal communication, 2006).

#### **MRSA infection-related interventions and treatment intensity**

Superficial MRSA infections are treated with intravenous vancomycin. Deep or joint MRSA infections are treated with intravenous vancomycin and oral rifampicin<sup>4</sup> (Kay P, Consultant Orthopaedic Surgeon: personal communication, 2006).

Patients who develop an MRSA infection will require isolation and barrier nursing in addition to the interventions described above. Published UK estimates of the resource use associated with this suggest the following (*Table 15*).<sup>104</sup>

During an MRSA infection, patients would be barrier nursed in a side room, and will be discharged from hospital when they are MRSA negative. *Table 16* summarises treatment pathways and mortality for non-MRSA and MRSA SSIs post hip arthroplasty.

## **Results**

### **Baseline infection rates**

In the model, the baseline MRSA SSI rates and non-MRSA rates with a cephalosporin were varied

**TABLE 15** Isolation (barrier nursing) costs<sup>104</sup>

Cost component	Resource use	Cost <sup>a</sup>
Barrier nursing costs per day	[gloves (£0.02) + paper gown (£1.95) + 1 minute labour (£0.16)] multiplied by 144 room entries per day	£306.93 per day (2002 prices); inflated to 2005: £348.27 <sup>39</sup>

<sup>a</sup> Source: Royal Free Hospital, London.

**TABLE 16** Treatment pathways and mortality attributable to infection

Type of SSI	Treatment <sup>107</sup>	Mean length of stay (days) (95% CI) <sup>2</sup>	30 day mortality (%) <sup>2</sup>
No SSI	None	11.1	2.4
Superficial SSI	Antibiotic treatment with: Non-MRSA: erythromycin MRSA: vancomycin <sup>4</sup> plus barrier nursing	20.0 (18.8 to 21.3)	5.7
Deep or joint SSI	Exploration, debridement and washout, antibiotic treatment with: Non-MRSA: erythromycin MRSA: vancomycin and rifampicin <sup>4</sup> plus barrier nursing	33.9 (30.3 to 38.0)	11.9

**TABLE 17** Treatment effect<sup>17</sup>

Option	Event	r	N	p (%)	Odds	OR
Vancomycin	MRSA infection	2	452	0.44	0.0044	0.2705
	Non-MRSA infection	41	452	9.07	0.0998	1.2501
Cephalosporin	MRSA infection	7	433	1.62	0.0164	
	Non-MRSA infection	32	433	7.39	0.0798	

from 0 to 1% and from 0 to 3%, respectively. The baseline MRSA SSI rate was not a direct input to the model but was varied to find the threshold. To put this range in context, the mean overall SSI and MRSA SSI rates for hip arthroplasty in England are 2.23%<sup>2</sup> and 0.54%, respectively.

### Treatment effect of glycopeptides

Only two studies in the systematic effectiveness review captured cases of MRSA (see Chapter 3).<sup>16,17</sup> That by Kitzis and colleagues was a smaller study and only available in abstract form.<sup>16</sup> Therefore, the treatment effect was obtained from Finkelstein and colleagues' study of vancomycin versus cefazolin prophylaxis for cardiac surgery in the setting of a high prevalence of methicillin-resistant staphylococcal infections,<sup>17</sup> as summarised in Table 17.

Mortality data<sup>2</sup> were combined with published utility weights<sup>106</sup> and life expectancy estimates

([http://www.gad.gov.uk/Life\\_Tables/Interim\\_life\\_tables.htm](http://www.gad.gov.uk/Life_Tables/Interim_life_tables.htm)) to derive an estimate of effect of SSI on mortality and QALY production, as summarised in Table 18.

### Resource use and unit costs

The resource use and costs associated with the following sections of the model were developed based on the following (see Tables 19 and 20):

- vancomycin prophylaxis
- cephalosporin prophylaxis
- inpatient hip arthroplasty episode
- management of superficial and deep/joint non-MRSA and MRSA infections.

### Incremental cost-effectiveness

Table 21 summarises the effect of SSI, including type of SSI (superficial or deep/joint), on costs, QALYs and the average (mean) number of days' use of glycopeptides. Table 22

**TABLE 18** Effect of SSI on mortality and QALYs

Event	QALY	Sub-event	Probability	QALY	Loss due to hospital stay
No infection	8.53	Death	0.024	0.00	0.0000
		Alive	0.976	8.74	
Superficial infection	8.24	Death	0.057	0.00	0.0030
		Alive	0.943	8.74	
Deep/joint infection	7.70	Death	0.119	0.00	0.0063
		Alive	0.881	8.74	

**TABLE 19** Treatment pathways and costs

Resource use	Units	Cost (£)	Source
<b>Treatment pathway and cost of vancomycin prophylaxis</b>			
Vancomycin prophylaxis 1 g b.d. for 24 h (BOA)	2	32.22	<a href="http://www.boa.ac.uk/PDF%20files/BOA%20Hip%20replacement.pdf">http://www.boa.ac.uk/PDF%20files/BOA%20Hip%20replacement.pdf</a>
Administration costs: 100 ml of 0.9% sodium chloride solution	2	0.60	SPC (electronic Medicines Compendium)
Total		32.82	
<b>Treatment pathway and cost of cephalosporin prophylaxis</b>			
Cefuroxime prophylaxis 1.5 g at induction, followed by 2 doses of 750 mg (4 ampoules 750 mg) (BOA/BNF)	4	18.80	<a href="http://www.boa.ac.uk/PDF%20files/BOA%20Hip%20replacement.pdf">http://www.boa.ac.uk/PDF%20files/BOA%20Hip%20replacement.pdf</a>
Administration costs: 10 ml of water for injection	3	0.93	SPC (electronic Medicines Compendium)
Total		19.73	
<b>Treatment pathway and cost of a hip arthroplasty episode</b>			
Hip arthroplasty episode	1	6060.60	NHS reference costs; <a href="http://www.dh.gov.uk/">http://www.dh.gov.uk/</a>
<b>Treatment pathway and cost of superficial non-MRSA infection</b>			
Non-MRSA antibiotic treatment with erythromycin 500 mg q.d.s. for 7 days	28	5.32	Personal communication (P Kay, Consultant Orthopaedic Surgeon)
Administration costs: none	0	0.00	SPC (electronic Medicines Compendium)
MRSA test	1	7.09	NHS reference costs; <a href="http://www.dh.gov.uk/">http://www.dh.gov.uk/</a>
Inpatient day	8.9	1780.00	Coello, 2005 <sup>2</sup>
Total		1792.41	
<b>Treatment pathway and cost of deep/joint non-MRSA infection</b>			
Non-MRSA antibiotic treatment with erythromycin 500 mg q.d.s. for 14 days	56	10.64	Personal communication (P Kay, Consultant Orthopaedic Surgeon)
Administration costs:none	0	0.00	SPC (electronic Medicines Compendium)
MRSA test	1	7.09	NHS reference costs; <a href="http://www.dh.gov.uk/">http://www.dh.gov.uk/</a>
Inpatient day	22.8	4560.00	Coello, 2005 <sup>2</sup>
Wound exploration	1	1107.00	Blom, 2004 <sup>108</sup>
Total		5684.73	

BOA, British Orthopaedic Association.

**TABLE 20** Unit costs used in the model

Item	Unit cost (£)	Source
Vancomycin 1 g injection	16.11	BNF 50
100 ml 0.9% sodium chloride solution	0.30	Local NHS contract cost
Teicoplanin 400 mg injection	35.62	BNF 50
Cefuroxime 1.5 g injection	4.70	BNF 50
Cefuroxime 750 mg injection	2.34	BNF 50
Water for injection 10 ml	0.31	BNF 50
Cost per orthopaedic stay including hip arthroplasty	6060.60	NHS reference costs; <a href="http://www.dh.gov.uk/">http://www.dh.gov.uk/</a>
Inpatient day for orthopaedic surgical patient	200.00	NHS reference costs
MRSA test	7.09	NHS reference costs
Barrier nursing <sup>a</sup>	348.27	Kunori, 2002 <sup>104</sup>
Wound exploration <sup>b</sup>	1107.00	NHS reference costs; <a href="http://www.dh.gov.uk/">http://www.dh.gov.uk/</a>
Rifampicin 300 mg capsule	0.60	BNF 50
Erythromycin 500 mg tablets	0.19	BNF 50

<sup>a</sup> Hospital and Community Health Services inflated from 2002 to 2005.  
<sup>b</sup> Health Related Group Code (H17) Soft Tissue or Other Bone Procedures – Category 1 <70 without complications.

**TABLE 21** Effect of SSI on cost, QALYs and the number of days' use of glycopeptides

Event	Cost (£)	QALYs	Glycopeptide use (days)	Sub-event	Probability	Cost (£)	QALYs	Glycopeptide use (days)
No infection	6,061	8.53	0.00					
MRSA infection	11,104	7.44	7.09	Superficial	0.807	11,177	8.24	7
				Deep/joint	0.103	20,235	7.70	14
Other infection	7,547	7.44	0.00	Superficial	0.807	7,853	8.24	0
				Deep/joint	0.103	11,745	7.70	0

**TABLE 22** Effect of treatment options on cost, QALYs and days' use of glycopeptide

Option		Cost (£)	QALYs	Glycopeptide use (days)	Individual events (mutually exclusive)				
					Event	Probability	Cost (£)	QALYs	Glycopeptide use (days)
Vancomycin	Treatment	32.82	0	1	No infection	0.986	6,061	8.53	0.00
	Event	6,086	8.52	0.01	MRSA alone	0.001	11,104	7.44	7.09
	Total	6,119	8.52	1.01	Other alone	0.012	7,547	7.44	0.00
					MRSA + other	0.000	11,104	7.44	7.09
Cephalosporin	Treatment	19.73	0	0	No infection	0.985	6,061	8.53	0.00
	Event	6,101	8.52	0.04	MRSA alone	0.005	11,104	7.44	7.09
	Total	6,120	8.52	0.04	Other alone	0.010	7,547	7.44	0.00
					MRSA + other	0.000	11,104	7.44	7.09
Cephalosporin and vancomycin	Treatment	52.55	0	0	No infection	0.989	6,061	8.53	0.00
	Event	6,082	9	0.01	MRSA alone	0.001	11,104	7.44	7.09
	Total	6,135	8.52	0.01	Other alone	0.010	7,547	7.44	0.00
					MRSA + other	0.000	11,104	7.44	7.09

summarises the effect of the different treatment options on costs, QALYs and the average (mean) number of days' use of glycopeptides. This table also includes data on the probability of infection for each type of treatment option. Both tables summarise the data detailed in the previous three sections.

The incremental cost-effectiveness analysis examined the relative cost-effectiveness of vancomycin, cephalosporin and a combination of the cephalosporin with vancomycin. The indicative model was populated with the data detailed in *Tables 21* and *22*. Assuming a cost-effectiveness threshold of £30,000 per QALY gained, an expected net benefit for each option was calculated for a range of baseline MRSA SSI rates and non-MRSA rates: 0–1.0% and 0–3.0%, respectively. This analysis identified the optimal choice of prophylaxis (vancomycin, cephalosporin or cephalosporin and vancomycin) at each level of infection rates, as summarised in *Table 23*.

The purpose of the analysis is to show the sort of modelling that could be undertaken if the complexities and evidence limitations discussed in the section 'Purpose' (p. 64) can be overcome. However, the relationship between the indicative results presented here and underlying infection risk is useful to understand. These results suggest that a cephalosporin alone is only optimal (1) when the other infection rate is 0% or (2) when the MRSA infection rate is  $\geq 0.2\%$  and the other infection rate is  $\leq 0.1\%$ . Vancomycin alone is only optimal (1) where the MRSA infection rate is  $\leq 0.15\%$  and the other infection rate is 0.1% or (2) if the MRSA infection rate is  $\leq 0.2\%$  and the other infection rate is  $\geq 0.2\%$ . If the MRSA infection rate is  $\geq 0.25\%$  and the other infection rate is  $\geq 0.2\%$ , the combination of cephalosporin plus vancomycin is optimal.

The total glycopeptide use for each treatment option was also estimated as reported in *Table 24*. This showed that, up to a baseline MRSA infection rate of between 20 and 25%, use of antibiotic

**TABLE 23** Details of the optimal form of prophylaxis [vancomycin (V), cephalosporin (C) or cephalosporin plus vancomycin (CV)] for a given combination of baseline MRSA infection rate and other infection rate, assuming a threshold cost-effectiveness of £30,000 per QALY gained

Other infection rate: CV (%)	MRSA infection rate (%)													
	0	0.05	0.10	0.15	0.20	0.25	0.30	0.40	0.50	0.60	0.70	0.80	0.90	1.00
0.0	C	C	C	C	C	C	C	C	C	C	C	C	C	C
0.1	V	V	V	V	C	C	C	C	C	C	C	C	C	C
0.2	V	V	V	V	V	CV	CV	CV	CV	CV	CV	CV	CV	CV
0.3	V	V	V	V	V	CV	CV	CV	CV	CV	CV	CV	CV	CV
0.4	V	V	V	V	V	CV	CV	CV	CV	CV	CV	CV	CV	CV
0.5	V	V	V	V	V	CV	CV	CV	CV	CV	CV	CV	CV	CV
1.0	V	V	V	V	V	CV	CV	CV	CV	CV	CV	CV	CV	CV
1.5	V	V	V	V	V	CV	CV	CV	CV	CV	CV	CV	CV	CV
2.0	V	V	V	V	V	CV	CV	CV	CV	CV	CV	CV	CV	CV
2.5	V	V	V	V	V	CV	CV	CV	CV	CV	CV	CV	CV	CV
3.0	V	V	V	V	V	CV	CV	CV	CV	CV	CV	CV	CV	CV

**TABLE 24** Expected use for each treatment option

	Baseline MRSA rate (%)										
	0	5	10	15	20	25	30	35	40	45	50
Expected glycopeptide use with vancomycin prophylaxis	0	0.354	0.709	1.064	1.418	1.773	2.127	2.482	2.836	3.191	3.546
Expected glycopeptide use with cephalosporin prophylaxis	1	1.100	1.207	1.323	1.449	1.586	1.737	1.902	2.083	2.285	2.510

prophylaxis is not glycopeptide sparing. That is, up to these rates, the total use of glycopeptides (for prophylaxis and for treatment) is greater than when glycopeptides are used only for treatment. This might be expected to have significant implications for drug resistance over the longer term.

## Discussion

This study set out to examine whether there is a threshold value for prevalence of MRSA that favours routine prophylaxis with glycopeptide antibiotics.

In order to answer this question, we developed an economic model, using hip arthroplasty by way of an exemplar. However, it is clear from the clinical evidence presented in Chapter 3 and the economic reviews in Chapters 4 and 5 that such a modelling exercise could only be indicative in nature. To address fully the cost-effectiveness of glycopeptides as surgical antibiotic prophylaxis would need a much more extensive evidence

gathering, synthesis and modelling initiative than has been possible in this review. The characteristics of such a research programme are described in Chapter 7.

Despite the model being indicative rather than definitive, it shows the approach that would be possible given appropriate evidence. It can be used to show the threshold baseline risk of MRSA infection at which a particular intervention (here glycopeptides as prophylaxis) might be cost-effective. This involves estimating a treatment effect of the intervention on that baseline risk, incorporating its acquisition cost and those of its comparators and quantifying the implications of the various types of infections in terms of resource costs and quality-adjusted survival duration. An important feature of this modelling framework is the interpretation of the baseline risk threshold. As presented here, it relates to an average risk of MRSA SSI in the population of patients undergoing hip arthroplasty in a given centre. However, this baseline risk can also be seen at the level of the individual patient. Using a multivariable risk model, the baseline risk of

infection in an individual patient can be predicted based on patient-level characteristics such as previous infections, age and co-morbidities such as presence of decubitus ulcer or history of previous hospitalisation, in addition to centre-level characteristics.<sup>109</sup> Such an interpretation can also incorporate the effect of MRSA screening, which effectively changes a baseline (prior) probability of infection based on a population average into a revised (posterior) probability of infection.

Although the model results presented here are of little direct policy relevance, the indicative model suggests that, where the MRSA infection rate is  $\geq 0.25\%$  and the rate of other infections with cephalosporin prophylaxis is  $\geq 0.2\%$ , the combination of cephalosporin plus vancomycin is the optimal antibiotic prophylaxis for hip arthroplasty patients. These results are not very surprising because vancomycin is very similar in cost to the standard cephalosporin, cefuroxime, but the limited evidence available seems to suggest that vancomycin is more effective in preventing MRSA infections. Furthermore, the combination arm has been assumed to have an additive effect. There is a mortality reduction associated with infection rate reduction. The cost of the antibiotics alone contributed little to overall costs and there was relatively little difference in cost across antibiotics used. In MRSA-infected patients, hospital discharge was delayed between 8 and 23 days, on average, with substantial cost implications. Therefore, a small decrease in attributable mortality would, on average, typically

be expected to offset the cost of the antibiotic prophylaxis. Therefore, by reducing the rate of MRSA infection, vancomycin generates a gain in quality-adjusted life expectancy compared with cefuroxime; the combination strategy generates an even greater gain. As a result, in the indicative model, the baseline risk of MRSA can be modest (below the national average) and it would still appear cost-effective to use glycopeptides.

However, this conclusion is reached in the absence of any explicit modelling of the effect of greater use of glycopeptides on drug resistance. Little is known about current levels of resistance, the rate of development of resistance transmission rates and the impact of interventions on resistance. Therefore, like all modelling undertaken in this and related areas (see Chapters 4 and 5), no attempt has been made explicitly to reflect future resistance in the model. The model does indicate that, at all plausible baseline infection rates, the use of glycopeptides as a form of prophylaxis, in addition to a treatment of infections, will increase the total use of the drug. Therefore, even if the argument is accepted that the risk of resistance is directly proportional to total antibiotics usage and the argument that the shorter courses of antibiotics used in prophylaxis are more likely to lead to resistance than the longer therapeutic courses is discounted, prophylactic use of glycopeptides is unlikely to decrease total usage and so decrease the risk of resistance problems in the future.





# Chapter 7

## Discussion

The aim of this project was to determine whether there is a level of MRSA prevalence at which a switch from non-glycopeptide to glycopeptide antibiotics for routine prophylaxis is indicated in surgical environments with a high risk of MRSA infection. To answer this question, a systematic review of the clinical effectiveness and cost-effectiveness of glycopeptide prophylaxis was undertaken, and a decision analytic model investigating the cost-effectiveness of glycopeptides in relation to MRSA prevalence was developed. The systematic reviews provided little evidence for the clinical effectiveness or cost-effectiveness of glycopeptides for MRSA prophylaxis. No cost-effectiveness studies and only two trials were conducted in the UK, which limits their generalisability. There was also a lack of recent evidence, as most of the studies were conducted prior to 2001. This confirms the conclusions of Glenny and Song, who conducted a systematic review in 1998 of antimicrobial prophylaxis for total hip replacement and concluded that the volume of research in this area was decreasing.<sup>110</sup>

Most studies identified in the effectiveness review did not report the prevalence of MRSA or the incidence of MRSA infections as an outcome. With one exception, a trial of cardiac surgery conducted in a hospital in Israel with a high MRSA prevalence,<sup>17</sup> the trials were not designed primarily to address MRSA prevention. This meant that the systematic review was unable to link the effectiveness of glycopeptide prophylaxis to different MRSA prevalence levels.

It was not possible to undertake definitive modelling of cost-effectiveness within the scope of this project, given the lack of clinical evidence and major complexities, such as the choice of prophylaxis and treatment options and the high-level uncertainty about future development of resistance. Instead, an indicative cost-effectiveness model was developed which focused on a single surgical specialty. Hip arthroplasty was chosen as an exemplar, as it is a clean procedure, patients are at high risk of infection (including MRSA), and it was expected that more data would be available compared with other surgical specialties. However, this model is indicative only and

considers vancomycin but not teicoplanin prophylaxis. Given that the relevant evidence is so scant and the problem of modelling resistance so complex, this emphasises the care required in formalising policy in the context of resistance.

It is hoped that this indicative modelling framework will contribute to future research in this area in a number of ways. It shows how available evidence on a range of baseline infection risks, acquisition costs and treatment effects of alternative anti-infection interventions, and the costs and health consequences of infection can be brought together to inform decisions about the relative cost-effectiveness of these options as a function of baseline risks. Although the indicative model here was developed in the exemplar area of hip arthroplasty, the framework has relevance to a range of surgical areas including other 'clean' procedures such as vascular surgery, which, like orthopaedic surgery, is high-volume surgery and is increasingly performed in older, sicker patients who are more likely to be MRSA carriers. The model structure would have to be adjusted in contaminated procedures such as gastrointestinal surgery, where the presence of bacteria means that patients may be classified as 'infected' prior to the procedure.

Our indicative model concentrates on the use of vancomycin compared with cephalosporin prophylaxis in primary hip arthroplasty. However, most orthopaedic procedures are now carried out in specialist 'clean-air' suites that reduce the need for anti-MRSA prophylaxis. This is not necessarily the case for other types of surgery. Joint replacement patients are considered to be 'high-risk' patients, as an infection could have serious long-term consequences requiring revision surgery. Despite patient, manager and infection control teams' concerns about MRSA, this may not be the major concern for surgeons in orthopaedic surgery as evidence suggests that MRSE infections are more of a problem in failed joint replacements<sup>101</sup> (Kay P, Campbell P, Consultant Orthopaedic Surgeons: personal communication, 2006) suggesting that focusing on MRSA may be too narrow a focus in areas other than orthopaedic surgery.

More fundamentally, the mechanisms of development of resistance may be affected by the type of surgical procedure. The use of vancomycin in gastrointestinal surgery has been reported to promote the development of VRE, and this resistant strain is known to pass on its genes to *S. aureus*, thus cultivating VRSA.<sup>111,112</sup> This mechanism has not been reported in clean surgery. The supplementary reviews conducted to assist with the modelling of antibiotic resistance found indicative models only where the methods varied according to disease type. In addition, no models were identified which could prospectively predict changes in the rate of the development of resistance in the global clinical population resulting from changes in treatment practice. These reviews did not provide any insights into how to model cost-effectiveness in the context of resistance. Given the constraints of the project, we were unable to incorporate the emergence of glycopeptide resistance in our model, and so could not fully explore its impact upon the use of glycopeptides as prophylaxis. However, our model indicates that, over all baseline MRSA prevalence rates, increasing the use of glycopeptide prophylaxis is likely to increase the risk of future resistance problems, if we assume that increased environmental exposure to glycopeptides is one of the factors that increase prevalence of resistance.

### Development of a model to guide surgical antibiotic prophylaxis prescribing

The research need that led to this project was the development of a model that identifies an MRSA prevalence rate, or series of rates, dependent on other risk variables, which will inform practitioners whether a particular set of patient, environmental and procedural variables suggest that a patient, or patient group, should have glycopeptide surgical prophylaxis.

Development of a model or algorithm which could be used by a clinician to guide surgical antibiotic prophylaxis prescribing would have substantial clinical application. The combination of reviews and modelling carried out in this study suggests that such a model would require a number of inputs. Current uncertainty about the nature of those inputs, instability of these over time and complexity of the relationship of those inputs suggest that the development of a full model, or clinical algorithm, would require a lengthy consultation process with interested

groups. Practically, it would be difficult to define an MRSA threshold for a particular hospital. Discussion with clinical experts has suggested that an individual patient's risk of infection would be more useful for decision-making as the idea that a whole specialty would change its prophylaxis policy for all patients on the basis of an average infection rate, which may be out of date by the time the decision is taken, may be unrealistic. The hospital's ward-based and perioperative infection control policies, including MRSA screening, are factors affecting an individual patient's risk of an infection. If a hospital has a high MRSA prevalence, this is indicative of a failure of infection control systems, and suggests that they need to take other actions to improve those systems. If rates are high, or there is an outbreak, then wards or surgeries should be temporarily closed; increasing glycopeptide use will not be the solution. A policy or clinical algorithm should not just advocate the use of glycopeptide prophylaxis in this scenario.

### Recommendations for practice

Due to the lack of available evidence about the effectiveness of glycopeptide prophylaxis, and complexities relating to the range of potential management options, we have been unable to develop a definitive decision analytic model which could be used by surgical centres to guide antibiotic prophylaxis choice. Our indicative model of the choice between vancomycin and cephalosporin prophylaxis in hip arthroplasty illustrates when vancomycin is likely to be most cost-effective based on varying baseline MRSA and other non-MRSA infection rates. However, this is an illustrative model only and inevitably provides only limited policy guidance. It does show that the use of glycopeptide prophylaxis is unlikely to reduce future overall exposure and may increase the risk of future resistance problems. The new British Society for Antimicrobial Chemotherapy guidelines<sup>4</sup> recommend that glycopeptides (alone or with other antibiotics) should be given to patients with a history of MRSA colonisation, or infections without documented eradication, or have come from a facility with a high prevalence of MRSA. This patient-based risk approach, combined with knowledge of local resistance patterns, may be the most appropriate approach to use of glycopeptides in surgical prophylaxis, given current uncertainties around the effectiveness of glycopeptides, development of resistance and impact of glycopeptides on resistance patterns.

## Recommendations for research

This review highlights the complexities of decision-making relating to infection control in general and of MRSA control in particular. As yet, the full mechanism of resistance is not fully understood. Microbiologists and epidemiologists in the field are likely to provide an important contribution in furthering this understanding. Their research expertise could provide a useful precursor to further economic modelling work.

- Research to inform decisions in this area needs to reflect these complexities and adopt analytical methods which can handle them. One implication of this is that a focus on MRSA, rather than a broader consideration of infections in general, is too limited. Although the media may present it as otherwise, there seems to be little basis to justify MRSA being a priority in terms of prevalence or the severity of its sequelae, and future research needs to place MRSA in a broader context of infection control. Similarly, as highlighted in the fourth literature review in Chapter 5 ('A conceptual framework for the economic evaluation of policies against MRSA', p. 56), there is a large number of possible infection control policies which can be used in the presence of infection problems (MRSA or otherwise), and the prophylactic use of glycopeptides is only one of these. The results of this project suggest that the **clinical** evidence about glycopeptides in this context is limited. An investigation of whether other infection control policies would be more effective and cost-effective than prophylaxis is needed.
- A full evidence synthesis and modelling study to inform wider decision-making in infection control is warranted, given a suitable budget and timetable. Such a study would aim to define the complete range of interventions and policies used in infection control for MRSA but also extending to other infections. This would need to include hospital- or department-wide policies such as bed configuration and screening and also interventions for individual patients such as prophylactic antibiotics. It would be necessary to bring together a wider evidence base to inform this comparison, and to include suitably elicited opinion from appropriate experts. The use of interdisciplinary collaboration would help to pursue the research agenda and to make use of the wide evidence base. For example, expertise developed in biostatistical modelling, such as in HIV/AIDS, could be highly relevant, in terms of both methods and sources of data used. The results from this research would inform both policy and priorities for primary research in this area.
- As this review has highlighted, a lack of evidence about the clinical effectiveness of glycopeptide prophylaxis for MRSA, a large multi-centre trial or cluster randomised trial is needed to address effectiveness across surgical centres with varying levels of MRSA prevalence. This could then be used to aid the development of a full decision analytic model. However, as rates of post-surgical MRSA infections are generally very low (<1%), sample sizes would have to be large (for example, to detect a reduction in MRSA rates from 1 to 0.5% at a power of 80% would require approximately 9000 patients). An alternative strategy would be to perform a cluster randomised trial, with surgical units being randomised to a particular regimen rather than individual patients, although this would require a larger sample size than an equivalent patient-level RCT. As such a trial may be difficult to conduct, a feasibility project could be undertaken by surveying surgeons across different specialties to identify if they would be willing to participate.
- However, such a trial may not be the best option for future research as by the time the results were available they may no longer be of importance in the light of new anti-MRSA treatments currently in development. Given the paucity of clinical effectiveness data and the problems that undertaking trials in this area may present, it would be worth devoting research effort to see whether other non-experimental data could provide useful information.
- Measuring the development and patterns of resistance to glycopeptides requires further long-term research over many years and surveillance of the incidence of glycopeptide-resistant bacteria, rather than through the medium of RCTs, which are suited to hypothesis testing, not characterisation or examination of complex longitudinal mechanisms. A research programme to predict the long-term pattern of drug resistance, its implications for future costs and health and the inter-sectoral, macro-economic and international effects relating to resistance is needed. Modelling resistance is further complicated by the fact that there are numerous strains of MRSA and they all develop resistance using different mechanisms. Such a research initiative would be relatively expensive and take some years to produce useful results, but it is essential before major additional resources are devoted to new primary research such as RCTs.



## Chapter 8

# Conclusions

There is not enough evidence available from RCTs to assist in decision-making about whether and when to change from non-glycopeptide to glycopeptide antibiotics for prophylaxis. There was also a lack of evidence about the cost-effectiveness of glycopeptide antibiotic prophylaxis.

Due to the lack of available evidence about the effectiveness of glycopeptide prophylaxis, and complexities relating to the range of potential management options, we were unable to develop a definitive decision analytic model. The indicative economic model developed using hip arthroplasty as a surgical exemplar shows how available evidence on a range of baseline infection risks, the acquisition costs and treatment effects of alternative anti-infection interventions and the costs and health consequences of infection can be brought together to inform decisions about the relative cost-effectiveness of these options as a

function of baseline risks. The findings of the indicative model do not support the case for using glycopeptides prophylactically rather than therapeutically.

There is a lack of available trial data reporting the incidence of glycopeptide-resistant bacteria, and no economic models incorporating resistance were identified. The impact of antibiotic resistance on the wider population was not incorporated into the economic model. There is very large uncertainty in terms of the impact of antibiotic resistance, surgeons and hospitals risk aversion to resistance and substantial variation in hospital infection control procedures across the UK, all of which would need to be incorporated into a 'full' economic model. The modelling of bacterial resistance is an extremely complex issue encompassing the effects of time, drug use and patterns of transmission and was beyond the scope of this project, given its short duration.





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### Contribution of authors

Gillian Cranny (Research Fellow) worked on the systematic review of effectiveness and was responsible for writing the protocol, study selection, data extraction, validity assessment and report writing. Rachel Elliott (Clinical Senior Lecturer) was responsible for the cost-effectiveness review of non-glycopeptide antibiotic prophylaxis for surgery and the cost-effectiveness review of antibiotics where antibiotic resistance is a problem. She was involved in the selection of studies, data extraction, quality assessment and report writing, and also in the development of the economic model. She contributed clinical and pharmacological expertise to the background

section and the effectiveness section. Helen Weatherly (Research Fellow) was responsible for the cost-effectiveness review of glycopeptide antibiotics compared with appropriate comparators. She was involved in the selection of studies, data extraction and quality assessment, all the cost-effectiveness reviews, report writing and in the development of the economic model. Duncan Chambers (Research Fellow) worked on the systematic review of effectiveness and was responsible for writing the protocol, study selection, data extraction, validity assessment and report writing. Neil Hawkins (Research Fellow) was responsible for the review of the use of epidemiological and decision-analytic techniques to model antibiotic resistance in addition to being responsible for the economic model. He was involved in the selection of studies, data extraction and report writing. Lindsey Myers (Information Officer) devised the search strategy, carried out the literature searches and contributed to report writing. Mark Sculpher (Professor of Health Economics) provided input at all stages. He was responsible for writing the section on a conceptual framework for the economic evaluation of policies against MRSA and the discussion sections. He commented on the design of the economic model and on various drafts of the report. Alison Eastwood (Senior Research Fellow) provided input at all stages, commented on various drafts of the report and had overall responsibility for the clinical effectiveness review.







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# Appendix I

## Search strategy

This appendix presents the detailed searches carried out to inform the review and the economic model.

### Effectiveness review

The core search strategy used for this review was as follows:

1. Vancomycin/
2. 1404-90-6.rn.
3. vancomycin.ti,ab.
4. vancocin.ti,ab.
5. lyphocin.ti,ab.
6. vancoled.ti,ab.
7. vancor.ti,ab.
8. Teicoplanin/
9. 61036-62-2.rn.
10. teicoplanin.ti,ab.
11. teichomycin\$.ti,ab.
12. targocid.ti,ab.
13. exp Glycopeptides/
14. Antibiotics, Glycopeptide/
15. glycopeptide\$.ti,ab.
16. Antibiotic Prophylaxis/
17. Premedication/
18. (antibiotic\$ adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab.
19. ((anti-microbial\$ or antimicrobial\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab.
20. ((anti-bacterial\$ or antibacterial\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab.
21. ((anti-mycobacterial\$ or antimycobacterial\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab.
22. ((bacteriocidal or bacteriocide\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab.
23. or/1-22
24. Bacterial Infections/
25. ((bacteri\$ or wound\$ or tissue\$ or prosthese\$) adj2 (infect\$ or contam\$)).ti,ab.
26. soft tissue infections/
27. prosthesis-related infections/
28. Sepsis/
29. sepsis.ti,ab.
30. (hospital\$ adj2 infect\$).ti,ab.
31. (mrsa or VISA or GISA or VRSA).ti,ab.
32. ((methicillin\$ or meticillin\$ or methycillin\$) adj resist\$).ti,ab.
33. Staphylococcaceae/
34. staphylococcus/
35. staphylococcus aureus/
36. staphylococcus epidermidis/
37. staphylococcus haemolyticus/
38. staphylococcus hominis/
39. staphylococc\$.ti,ab.
40. micrococcus pyogenes.ti,ab.
41. exp Staphylococcal Infections/
42. Gram-Positive Bacteria/
43. gram-positive bacterial infections/
44. gram-positive bacteri\$.ti,ab.
45. Gram-Positive Cocci/
46. gram-positive cocci.ti,ab.
47. Methicillin Resistance/
48. Methicillin/
49. Penicillin Resistance/
50. Drug Resistance, Microbial/
51. or/24-50
52. exp Surgical Procedures, Operative/
53. (surgery or surgical or operat\$).ti,ab.
54. (preoperat\$ or pre-operat\$).ti,ab.
55. (intraoperat\$ or intra-operat\$).ti,ab.
56. (perioperat\$ or peri-operat\$).ti,ab.
57. exp "Prostheses and Implants"/
58. (prothe\$ or implant\$).ti,ab.
59. (bypass or graft\$).ti,ab.
60. (resection or dissect\$ or incision\$).ti,ab.
61. (biopsy or biopsies).ti,ab.
62. amputat\$.ti,ab.
63. ((hip\$ or knee\$ or joint\$) adj (replac\$ or arthroplast\$)).ti,ab.
64. (c-section\$ or caesarean\$ or ceasarean\$ or cesarean\$ or caesarian\$ or ceasarian\$ or cesarian\$).ti,ab.
65. hysterectom\$.ti,ab.
66. abortion\$.ti,ab.
67. or/52-66
68. Surgical Wound Infection/
69. ((surgery or surgical) adj2 (infect\$ or contamin\$)).ti,ab.
70. ((postoperat\$ or post-operat\$) adj2 infect\$).ti,ab.
71. (incision\$ adj2 (infect\$ or contam\$)).ti,ab.
72. or/68-71
73. 23 and 51 and 67
74. 23 and 72

75. 73 or 74
76. limit 75 to yr="1990 - 2005"
77. Animals/
78. Humans/
79. 77 not (77 and 78)
80. 76 not 79
81. (editorial or historical article or letter).pt.
82. 80 not 81

This strategy was designed for searching MEDLINE through the Ovid interface and was adapted as appropriate for all other databases searched, taking into account differences in indexing terms and search syntax for each database.

Full details of all databases searched and search strategies are provided below.

### **MEDLINE: Ovid** **(<http://gateway.ovid.com/athens>)**

The MEDLINE search covered the date range 1990 to September 2005 (Week 1). The search was carried out on 19 September 2005 and identified 4062 records.

1. VANCOMYCIN/ (6227)
2. 1404-90-6.rn. (6227)
3. vancomycin.ti,ab. (9106)
4. vancocin.ti,ab. (12)
5. lyphocin.ti,ab. (0)
6. vancoled.ti,ab. (6)
7. vancor.ti,ab. (0)
8. Teicoplanin/ (1292)
9. 61036-62-2.rn. (1292)
10. teicoplanin.ti,ab. (1833)
11. teichomycin\$.ti,ab. (22)
12. targocid.ti,ab. (3)
13. exp Glycopeptides/ (35378)
14. Antibiotics, Glycopeptide/ (2650)
15. glycopeptide\$.ti,ab. (5862)
16. Antibiotic Prophylaxis/ (3945)
17. Premedication/ (9969)
18. (antibiotic\$ adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (7968)
19. ((anti-microbial\$ or antimicrobial\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (1496)
20. ((anti-bacterial\$ or antibacterial\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (319)
21. ((anti-mycobacterial\$ or antimycobacterial\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (11)
22. ((bacteriocidal or bacteriocide\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (0)
23. or/1-22 (61524)
24. Bacterial Infections/ (46266)
25. ((bacteri\$ or wound\$ or tissue\$ or prosthe\$) adj2 (infect\$ or contam\$)).ti,ab. (50156)
26. soft tissue infections/ (858)
27. prosthesis-related infections/ (3291)
28. Sepsis/ (7383)
29. sepsis.ti,ab. (34192)
30. (hospital\$ adj2 infect\$).ti,ab. (7731)
31. (mrsa or VISA or GISA or VRSA).ti,ab. (4478)
32. ((methicillin\$ or meticillin\$ or methycillin\$) adj resist\$).ti,ab. (7145)
33. Staphylococaceae/ (39)
34. staphylococcus/ (18264)
35. staphylococcus aureus/ (27303)
36. staphylococcus epidermidis/ (3496)
37. staphylococcus haemolyticus/ (25)
38. staphylococcus hominis/ (9)
39. staphylococc\$.ti,ab. (60096)
40. micrococcus pyogenes.ti,ab. (12)
41. exp Staphylococcal Infections/ (31180)
42. Gram-Positive Bacteria/ (5922)
43. gram-positive bacterial infections/ (3947)
44. gram-positive bacteri\$.ti,ab. (6983)
45. Gram-Positive Cocci/ (809)
46. gram-positive cocci.ti,ab. (2222)
47. Methicillin Resistance/ (5223)
48. Methicillin/ (2609)
49. Penicillin Resistance/ (9324)
50. Drug Resistance, Microbial/ (49349)
51. or/24-50 (257344)
52. exp Surgical Procedures, Operative/ (1436152)
53. (surgery or surgical or operat\$).ti,ab. (926821)
54. (preoperat\$ or pre-operat\$).ti,ab. (110649)
55. (intraoperat\$ or intra-operat\$).ti,ab. (46051)
56. (perioperat\$ or peri-operat\$).ti,ab. (26339)
57. exp "Prostheses and Implants"/ (222018)
58. (prosthe\$ or implant\$).ti,ab. (189473)
59. (bypass or graft\$).ti,ab. (174427)
60. (resection or dissect\$ or incision\$).ti,ab. (177550)
61. (biopsy or biopsies).ti,ab. (168204)
62. amputat\$.ti,ab. (17334)
63. ((hip\$ or knee\$ or joint\$) adj (replac\$ or arthroplast\$)).ti,ab. (20854)
64. (c-section\$ or caesarean\$ or ceasarean\$ or cesarean\$ or caesarian\$ or ceasarian\$ or cesarian\$).ti,ab. (23578)
65. hysterectom\$.ti,ab. (14956)
66. abortion\$.ti,ab. (30146)
67. or/52-66 (2282138)
68. Surgical Wound Infection/ (19970)
69. ((surgery or surgical) adj2 (infect\$ or contamin\$)).ti,ab. (6627)
70. ((postoperat\$ or post-operat\$) adj2 infect\$).ti,ab. (5381)

71. (incision\$ adj2 (infect\$ or contam\$)).ti,ab. (308)
72. or/68-71 (26955)
73. 23 and 51 and 67 (5475)
74. 23 and 72 (4201)
75. 73 or 74 (7222)
76. limit 75 to yr="1990-2005" (4432)
77. Animals/ (3795171)
78. Humans/ (8961704)
79. 77 not (77 and 78) (2905784)
80. 76 not 79 (4257)
81. (editorial or historical article or letter).pt. (924445)
82. 80 not 81 (4062)

**EMBASE: Ovid**  
(<http://gateway.ovid.com/athens>)

The EMBASE search covered the date range 1990 to 2005 (Week 37). The search was carried out on 19 September 2005 and identified 6580 records.

1. VANCOMYCIN/ (26284)
2. 1404-90-6.rn. (26378)
3. vancomycin.ti,ab. (9224)
4. vancocin.ti,ab. (15)
5. lyphocin.ti,ab. (0)
6. vancoled.ti,ab. (6)
7. vancor.ti,ab. (0)
8. Teicoplanin/ (5029)
9. 61036-62-2.rn. (5054)
10. teicoplanin.ti,ab. (2030)
11. teichomycin\$.ti,ab. (25)
12. targocid.ti,ab. (4)
13. Glycopeptide/ (3062)
14. exp polypeptide antibiotic agent/ (50141)
15. glycopeptide\$.ti,ab. (4757)
16. Antibiotic Prophylaxis/ (8434)
17. Premedication/ (5500)
18. (antibiotic\$ adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (7060)
19. ((anti-microbial\$ or antimicrobial\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (1416)
20. ((anti-bacterial\$ or antibacterial\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (279)
21. ((anti-mycobacterial\$ or antimycobacterial\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (14)
22. ((bacteriocidal or bacteriocide\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (1)
23. or/1-22 (71761)
24. Bacterial Infection/ (41468)
25. ((bacteri\$ or wound\$ or tissue\$ or prosthesis\$) adj2 (infect\$ or contam\$)).ti,ab. (40607)
26. Soft Tissue Infection/ (2337)
27. Prosthesis Infection/ (644)
28. Sepsis/ (29228)
29. sepsis.ti,ab. (29674)
30. (hospital\$ adj2 infect\$).ti,ab. (6281)
31. (mrsa or VISA or GISA or VRSA).ti,ab. (4372)
32. ((methicillin\$ or meticillin\$ or methycillin\$) adj resist\$).ti,ab. (7088)
33. Staphylococcaceae/ (5)
34. exp staphylococcus/ (50535)
35. staphylococc\$.ti,ab. (45241)
36. micrococcus pyogenes.ti,ab. (2)
37. Staphylococcus Infection/ (3901)
38. gram positive bacterium/ (12173)
39. gram-positive bacteri\$.ti,ab. (6246)
40. gram positive cocci/ (758)
41. gram-positive cocci.ti,ab. (1929)
42. antibiotic resistance/ (39148)
43. Meticillin/ (9160)
44. Penicillin Resistance/ (3059)
45. drug resistance/ (29683)
46. or/24-45 (234065)
47. exp surgery/ (1122365)
48. (surgery or surgical or operat\$).ti,ab. (720418)
49. (preoperat\$ or pre-operat\$).ti,ab. (93506)
50. (intraoperat\$ or intra-operat\$).ti,ab. (40440)
51. (perioperat\$ or peri-operat\$).ti,ab. (23970)
52. exp "prostheses and orthoses"/ (110394)
53. (prosthesis\$ or implant\$).ti,ab. (138687)
54. (bypass or graft\$).ti,ab. (147283)
55. (resection or dissect\$ or incision\$).ti,ab. (144691)
56. (biopsy or biopsies).ti,ab. (140919)
57. amputat\$.ti,ab. (13015)
58. ((hip\$ or knee\$ or joint\$) adj (replac\$ or arthroplast\$)).ti,ab. (17540)
59. (c-section\$ or caesarean\$ or ceasarean\$ or cesarean\$ or caesarian\$ or ceasarian\$ or cesarian\$).ti,ab. (19256)
60. hysterectom\$.ti,ab. (12939)
61. abortion\$.ti,ab. (16484)
62. or/47-61 (1681584)
63. Surgical Infection/ (2502)
64. ((surgery or surgical) adj2 (infect\$ or contamin\$)).ti,ab. (5608)
65. ((postoperat\$ or post-operat\$) adj2 infect\$).ti,ab. (4461)
66. (incision\$ adj2 (infect\$ or contam\$)).ti,ab. (236)
67. or/63-66 (11011)
68. 23 and 46 and 62 (7692)
69. 23 and 67 (2314)
70. 68 or 69 (8520)
71. limit 70 to yr="1990-2005" (6925)
72. Animal/ (15773)
73. Human/ (5003512)
74. 72 not (72 and 73) (12793)
75. 71 not 74 (6924)

76. (editorial or letter).pt. (438750)  
77. 75 not 76 (6580)

**CINAHL: Ovid**  
(<http://gateway.ovid.com/athens>)

The CINAHL search covered the date range 1990 to September 2005 (Week 2). The search was carried out on 19 September 2005 and identified 600 records.

1. VANCOMYCIN/ (315)
2. vancomycin.ti,ab. (602)
3. vancocin.ti,ab. (1)
4. lyphocin.ti,ab. (0)
5. vancoled.ti,ab. (0)
6. vancor.ti,ab. (0)
7. teicoplanin.ti,ab. (28)
8. teichomycin\$.ti,ab. (0)
9. targocid.ti,ab. (1)
10. Antibiotics, Peptide/ (19)
11. glycopeptide\$.ti,ab. (40)
12. Antibiotics/ (5226)
13. Antibiotic Prophylaxis/ (1108)
14. Premedication/ (240)
15. (antibiotic\$ adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (497)
16. ((anti-microbial\$ or antimicrobial\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (90)
17. ((anti-bacterial\$ or antibacterial\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (9)
18. ((anti-mycobacterial\$ or antimycobacterial\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (0)
19. ((bacteriocidal or bacteriocide\$) adj2 (prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)).ti,ab. (0)
20. or/1-19 (7110)
21. Bacterial Infections/ (1593)
22. ((bacteri\$ or wound\$ or tissue\$ or prosthesis\$) adj2 (infect\$ or contam\$)).ti,ab. (2079)
23. soft tissue infections/ (86)
24. prosthesis-related infections/ (53)
25. Sepsis/ (1390)
26. sepsis.ti,ab. (1594)
27. (hospital\$ adj2 infect\$).ti,ab. (1355)
28. (mrsa or VISA or GISA or VRSA).ti,ab. (820)
29. ((methicillin\$ or meticillin\$ or methycillin\$) adj resist\$).ti,ab. (746)
30. staphylococcus/ (214)
31. staphylococcus aureus/ (705)
32. staphylococc\$.ti,ab. (1618)
33. micrococcus pyogenes.ti,ab. (0)
34. exp Staphylococcal Infections/ (1664)
35. Gram-Positive Bacteria/ (100)
36. gram-positive bacterial infections/ (129)
37. gram-positive bacteri\$.ti,ab. (69)
38. gram-positive cocci.ti,ab. (67)
39. Methicillin Resistance/ (1142)
40. Methicillin/ (24)
41. Drug Resistance, Microbial/ (2696)
42. or/21-41 (11275)
43. exp Surgery, Operative/ (65532)
44. (surgery or surgical or operat\$).ti,ab. (43410)
45. (preoperat\$ or pre-operat\$).ti,ab. (3800)
46. (intraoperat\$ or intra-operat\$).ti,ab. (1382)
47. (perioperat\$ or peri-operat\$).ti,ab. (3042)
48. (prosthesis\$ or implant\$).ti,ab. (6316)
49. (bypass or graft\$).ti,ab. (5358)
50. (resection or dissect\$ or incision\$).ti,ab. (3051)
51. (biopsy or biopsies).ti,ab. (2412)
52. amputat\$.ti,ab. (1638)
53. ((hip\$ or knee\$ or joint\$) adj (replac\$ or arthroplast\$)).ti,ab. (1656)
54. (c-section\$ or caesarean\$ or ceasarean\$ or cesarean\$ or caesarian\$ or ceasarian\$ or cesarian\$).ti,ab. (2043)
55. hysterectom\$.ti,ab. (815)
56. abortion\$.ti,ab. (1374)
57. or/43-56 (96734)
58. Surgical Wound Infection/ (1374)
59. ((surgery or surgical) adj2 (infect\$ or contamin\$)).ti,ab. (718)
60. ((postoperat\$ or post-operat\$) adj2 infect\$).ti,ab. (256)
61. (incision\$ adj2 (infect\$ or contam\$)).ti,ab. (20)
62. or/58-61 (1766)
63. 20 and 42 and 57 (432)
64. 20 and 62 (345)
65. 63 or 64 (642)
66. limit 65 to yr="1990-2005" (617)
67. (editorial or historical material or letter).pt. (88413)
68. 66 not 67 (600)

**CENTRAL: The Cochrane Library**  
(CD-ROM issue 2005/3)

Issue 2005/3 of the Cochrane Library was searched to identify trials on the Cochrane Central Register of Controlled Trials (CENTRAL). The search was carried out on 20 September 2005, with the date range set at 1990 to date. The search identified 1473 trials.

1. VANCOMYCIN single term (MeSH) (301)
2. vancomycin (587)
3. vancocin (0)
4. lyphocin (0)
5. vancoled (1)
6. vancor (0)
7. TEICOPLANIN single term (MeSH) (136)

8. teicoplanin (207)
9. teichomycin\* (0)
10. targocid (0)
11. GLYCOPEPTIDES explode tree 1 (MeSH) (1027)
12. ANTIBIOTICS GLYCOPEPTIDE single term (MeSH) (123)
13. glycopeptide\* (259)
14. ANTIBIOTIC PROPHYLAXIS single term (MeSH) (590)
15. PREMEDICATION single term (MeSH) (2395)
16. ((antibiotic\* near prophyla\*) or (antibiotic\* near premedicat\*) or (antibiotic\* near pre-medocat\*) or (antibiotic\* near therapeutic\*)) (4428)
17. ((anti-microbial\* near prophyla\*) or (anti-microbial\* near premedicat\*) or (anti-microbial\* near pre-medocat\*) or (anti-microbial\* near therapeutic\*) or (antimicrobial\* near prophyla\*) or (antimicrobial\* near premedicat\*) or (antimicrobial\* near pre-medocat\*) or (antimicrobial\* near therapeutic\*)) (425)
18. ((anti-bacterial\* near prophyla\*) or (anti-bacterial\* near premedicat\*) or (anti-bacterial\* near pre-medocat\*) or (anti-bacterial\* near therapeutic\*) or (antibacterial\* near prophyla\*) or (antibacterial\* near premedicat\*) or (antibacterial\* near pre-medocat\*) or (antibacterial\* near therapeutic\*)) (2816)
19. ((anti-mycobacterial\* near prophyla\*) or (anti-mycobacterial\* near premedicat\*) or (anti-mycobacterial\* near pre-medocat\*) or (anti-mycobacterial\* near therapeutic\*) or (antimycobacterial\* near prophyla\*) or (antimycobacterial\* near premedicat\*) or (antimycobacterial\* near pre-medocat\*) or (antimycobacterial\* near therapeutic\*)) (0)
20. ((bacteriocidal near prophyla\*) or (bacteriocidal near premedicat\*) or (bacteriocidal near pre-medocat\*) or (bacteriocidal near therapeutic\*) or (bacteriocide\* near prophyla\*) or (bacteriocide\* near premedicat\*) or (bacteriocide\* near pre-medocat\*) or (bacteriocide\* near therapeutic\*)) (0)
21. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20) (9716)
22. BACTERIAL INFECTIONS single term (MeSH) (2448)
23. ((bacteri\* near infect\*) or (wound\* near infect\*) or (tissue\* near infect\*) or (prosthe\* near infect\*) or (bacteri\* near contam\*) or (wound\* near contam\*) or (tissue\* near contam\*) or (prosthe\* near contam\*)) (9624)
24. SOFT TISSUE INFECTIONS single term (MeSH) (29)
25. PROSTHESIS-RELATED INFECTIONS single term (MeSH) (73)
26. SEPSIS single term (MeSH) (392)
27. sepsis (2712)
28. (hospital\* near infect\*) (3306)
29. (mrsa or visa or gisa or vrsa) (145)
30. ((methicillin\* next resist\*) or (meticillin\* next resist\*) or (methycillin\* next resist\*)) (240)
31. STAPHYLOCOCCACEAE single term (MeSH) (0)
32. STAPHYLOCOCCUS explode tree 1 (MeSH) (599)
33. staphylococc\* (2248)
34. (micrococcus next pyogenes) (0)
35. STAPHYLOCOCCAL INFECTIONS explode tree 1 (MeSH) (680)
36. GRAM-POSITIVE BACTERIA single term (MeSH) (137)
37. GRAM-POSITIVE BACTERIAL INFECTIONS single term (MeSH) (143)
38. (gram-positive next bacteri\*) (380)
39. GRAM-POSITIVE COCCI single term (MeSH) (9)
40. (gram-positive next cocci) (113)
41. METHICILLIN RESISTANCE single term (MeSH) (110)
42. METHICILLIN single term (MeSH) (40)
43. PENICILLIN RESISTANCE single term (MeSH) (210)
44. DRUG RESISTANCE MICROBIAL single term (MeSH) (768)
45. (#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44) (14811)
46. SURGICAL PROCEDURES OPERATIVE explode tree 1 (MeSH) (50730)
47. (surgery or surgical or operat\*) (74595)
48. (preoperat\* or pre-operat\*) (10166)
49. (intraoperat\* or intra-operat\*) (6531)
50. (perioperat\* or peri-operat\*) (4142)
51. PROSTHESES AND IMPLANTS explode tree 1 (MeSH) (6015)
52. (prosthe\* or implant\*) (9161)
53. (bypass or graft\*) (12093)
54. (resection or dissect\* or incision\*) (7502)
55. (biopsy or biopsies) (7126)
56. amputat\* (720)
57. ((hip\* next replac\*) or (knee\* next replac\*) or (joint\* next replac\*) or (arthroplast\* next replac\*) or (hip\* next arthroplast\*) or (knee\* next arthroplast\*) or (joint\* next arthroplast\*) or (arthroplast\* next arthroplast\*)) (2662)

58. (c-section\* or caesarean\* or ceasarean\* or cesarean\* or caesarian\* or ceasarian\* or cesarian\*) (3532)
59. hysterectom\* (2159)
60. abortion\* (1642)
61. (#46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60) (104735)
62. SURGICAL WOUND INFECTION single term (MeSH) (1921)
63. ((surgery near infect\*) or (surgical near infect\*) or (surgery near contamin\*) or (surgical near contamin\*)) (3528)
64. ((postoperat\* near infect\*) or (post-operat\* near infect\*)) (1942)
65. ((incision\* near infect\*) or (incision\* near contam\*)) (136)
66. (#62 or #63 or #64 or #65) (4312)
67. (#21 and #45 and #61) (2270)
68. (#21 and #66) (1830)
69. (#67 or #68) (2489)
70. #69 ( 1990 to current date ) (1473)
71. ANIMALS single term (MeSH) (4802)
72. HUMANS check tag (MeSH) (260279)
73. (#71 and (not (#71 and #72))) (14)
74. (#70 and (not #73)) (1473)

### Science Citation Index: MIMAS Web of Science (<http://wok.mimas.ac.uk>)

The Science Citation Index search covered the date range 1990 to date. The search was carried out on 20 September 2005 and identified 2656 records.

1. TS=(vancomycin or vancocin or lyphocin or vancoled or vancor or teicoplanin or teichomycin\* or targocid or glycopeptide\*) (13733)
2. TS=((antibiotic\* or anti-microbial\* or antimicrobial\* or anti-bacterial\* or antibacterial\* or anti-mycobacterial\* or antimycobacterial\* or bacteriocidal or bacteriocide\*) same (prophyla\* or premedicat\* or pre-medicat\* or therapeutic\*)) (7736)
3. #2 OR #1 (20976)
4. TS=((bacteri\* or wound\* or tissue\* or prosth\*) same (infect\* or contam\*)) (59288)
5. TS=(sepsis or staphylococc\* or micrococcus pyogenes or gram-positive bacteri\* or gram-positive cocci) (75140)
6. TS=(hospital\* same infect\*) (11841)
7. TS=(mrsa or visa or gisa or vrsa or methicillin\* resist\* or meticillin\* resist\* or methycillin\* resist\*) (6775)
8. #7 OR #6 OR #5 OR #4 (>100000)

9. TS=(surgery or surgical or operat\* or preoperat\* or pre-operat\* or intraoperat\* or intra-operat\* or perioperat\* or peri-operat\*) (>100000)
10. TS=(prosth\* or implant\* or bypass or graft\* or resection or dissect\* or incision\* or biopsy or biopsies or amputat\*) (>100000)
11. TS=(hip\* replac\* or knee\* replac\* or joint\* arthroplast\* or hip\* arthroplast\* or knee\* arthroplast\* or joint\* arthroplast\*) (16290)
12. TS=(c-section\* or caesarean\* or ceasarean\* or cesarean\* or caesarian\* or ceasarian\* or cesarian\* or hysterectom\* or abortion\*) (37505)
13. #12 OR #11 OR #10 OR #9 (>100000)
14. TS=((surgery or surgical or incision\*) same (infect\* or contamin\*)) (9696)
15. TS=((postoperat\* or post-operat\*) same infect\*) (4928)
16. #15 OR #14 (13128)
17. #13 AND #8 AND #3 (2293)
18. #16 AND #3 (1457)
19. #18 OR #17 (2656)

### BIOSIS: Edina

(<http://edina.ac.uk/biosis/index.shtml>)

The BIOSIS search covered the date range 1990 to date. The search was carried out on 21 September 2005 and identified 1516 records and 329 records for the first and second search, respectively. The results from the two searches were de-duplicated in an endnote library, resulting in 1714 unique records.

Two separate searches were run on BIOSIS as the 'or' operator was not working at the time of searching.

### First search in Title/Subjects/Abstract

vancomycin or vancocin or lyphocin or vancoled or vancor or teicoplanin or teichomycin\* or targocid or glycopeptide\* or antibiotic\* n2 prophyla\* or antibiotic\* n2 premedicat\* or antibiotic\* n2 pre-medicat\* or antibiotic\* n2 therapeutic\* or anti-microbial\* n2 prophyla\* or anti-microbial\* n2 premedicat\* or anti-microbial\* n2 pre-medicat\* or anti-microbial\* n2 therapeutic\* or antimicrobial\* n2 prophyla\* or antimicrobial\* n2 premedicat\* or antimicrobial\* n2 therapeutic\* or anti-bacterial\* n2 prophyla\* or anti-bacterial\* n2 premedicat\* or anti-bacterial\* n2 pre-medicat\* or anti-bacterial\* n2 therapeutic\* or antibacterial\* n2 prophyla\* or antibacterial\* n2 premedicat\* or antibacterial\* n2 pre-medicat\* or antibacterial\* n2 therapeutic\* or anti-mycobacterial\* n2 prophyla\* or anti-mycobacterial\* n2 premedicat\* or anti-

mycobacterial\* n2 pre-medicat\* or antimycobacterial\* n2 therapeutic\* or antimycobacterial\* n2 prophyla\* or antimycobacterial\* n2 premedicat\* or antimycobacterial\* n2 pre-medicat\* or antimycobacterial\* n2 therapeutic\* or bacteriocidal n2 prophyla\* or bacteriocidal n2 premedicat\* or bacteriocidal n2 pre-medicat\* or bacteriocidal n2 therapeutic\* or bacteriocide\* n2 prophyla\* or bacteriocide\* n2 premedicat\* or bacteriocide\* n2 pre-medicat\* or bacteriocide\* n2 therapeutic\* (19300)

AND

bacteri\* n2 infect or wound\* n2 infect or tissue\* n2 infect or prosth\* n2 infect\* or bacteri\* n2 contam\* or wound\* n2 contam\* or tissue\* n2 contam\* or prosth\* n2 contam\* or sepsis or staphylococc\* or "micrococcus pyogenes" or gram-positive w bacteri\* or gram-positive w cocci or hospital\* n2 infect\* or mrsa or visa or gisa or vrsa or methicillin\* w resist\* or meticillin\* w resist\* or methycillin\* w resist\* (124606)

AND

surgery or surgical or operat\* or preoperat\* or pre-operat\* or intraoperat\* or intra-operat\* or perioperat\* or peri-operat\* or prosth\* or implant\* or bypass or graft\* or resection or dissect\* or incision\* or biopsy or biopsies or amputat\* or hip\* w replac\* or knee\* w replac\* or joint\* w replac\* or hip\* w arthroplast\* or knee\* w arthroplast\* or joint\* w arthroplast\* or c-section\* or caesarean\* or ceasarean\* or cesarean\* or caesarian\* or ceasarian\* or cesarian\* or hysterectom\* or abortion\* (915038)

### Second search in Title/Subjects/Abstract

vancomycin or vancocin or lyphocin or vancoled or vancor or teicoplanin or teichomycin\* or targocid or glycopeptide\* or antibiotic\* n2 prophyla\* or antibiotic\* n2 premedicat\* or antibiotic\* n2 pre-medicat\* or antibiotic\* n2 therapeutic\* or anti-microbial\* n2 prophyla\* or anti-microbial\* n2 premedicat\* or anti-microbial\* n2 pre-medicat\* or anti-microbial\* n2 therapeutic\* or antimicrobial\* n2 prophyla\* or antimicrobial\* n2 premedicat\* or antimicrobial\* n2 pre-medicat\* or anti-bacterial\* n2 prophyla\* or anti-bacterial\* n2 premedicat\* or anti-bacterial\* n2 pre-medicat\* or anti-bacterial\* n2 therapeutic\* or antibacterial\* n2 prophyla\* or antibacterial\* n2 premedicat\* or antibacterial\* n2 therapeutic\* or anti-mycobacterial\* n2 prophyla\* or anti-mycobacterial\* n2 premedicat\* or anti-mycobacterial\* n2 pre-medicat\* or anti-mycobacterial\* n2 therapeutic\* or antimycobacterial\* n2 prophyla\* or

antimycobacterial\* n2 premedicat\* or antimycobacterial\* n2 pre-medicat\* or antimycobacterial\* n2 therapeutic\* or bacteriocidal n2 prophyla\* or bacteriocidal n2 premedicat\* or bacteriocidal n2 pre-medicat\* or bacteriocidal n2 therapeutic\* or bacteriocide\* n2 prophyla\* or bacteriocide\* n2 premedicat\* or bacteriocide\* n2 pre-medicat\* or bacteriocide\* n2 therapeutic\* (19300)

AND

surgery n2 infect\* or surgical n2 infect\* or incision\* n2 infect\* or surgery n2 contamin\* or surgical n2 contamin\* or incision\* n2 contamin\* or postoperat\* n2 infect\* or post-operat\* n2 infect\* (1985)

### ISI Proceedings – Science and Technology edition: MIMAS Web of Science (<http://wok.mimas.ac.uk>)

The ISI Proceedings search covered the date range 1990 to date. The search was carried out on 22 September 2005 and identified 324 records.

1. TS=(vancomycin or vancocin or lyphocin or vancoled or vancor or teicoplanin or teichomycin\* or targocid or glycopeptide\*) (1257)
2. TS=((antibiotic\* or anti-microbial\* or antimicrobial\* or anti-bacterial\* or antibacterial\* or anti-mycobacterial\* or bacteriocidal or bacteriocide\*) same (prophyla\* or premedicat\* or pre-medicat\* or therapeutic\*)) (915)
3. #2 OR #1 (2119)
4. TS=((bacteri\* or wound\* or tissue\* or prosth\*) same (infect\* or contam\*)) (6558)
5. TS=(sepsis or staphylococc\* or micrococcus pyogenes or gram-positive bacteri\* or gram-positive cocci) (8186)
6. TS=(hospital\* same infect\*) (1405)
7. TS=(mrsa or visa or gisa or vrsa or methicillin\* resist\* or meticillin\* resist\* or methycillin\* resist\*) (767)
8. #7 OR #6 OR #5 OR #4 (14920)
9. TS=(surgery or surgical or operat\* or preoperat\* or pre-operat\* or intraoperat\* or intra-operat\* or perioperat\* or peri-operat\*) (>100000)
10. TS=(prosth\* or implant\* or bypass or graft\* or resection or dissect\* or incision\* or biopsy or biopsies or amputat\*) (88681)
11. TS=(hip\* replac\* or knee\* replac\* or joint\* replac\* or hip\* arthroplast\* or knee\* arthroplast\* or joint\* arthroplast\*) (2216)
12. TS=(c-section\* or caesarean\* or ceasarean\* or caesarian\* or ceasarian\* or

cesarian\* or hysterectom\* or abortion\*)  
(3823)

13. #12 OR #11 OR #10 OR #9 (>100000)
14. TS=((surgery or surgical or incision\*) same (infect\* or contamin\*)) (1329)
15. TS=((postoperat\* or post-operat\*) same infect\*) (715)
16. #15 OR #14 (1826)
17. #13 AND #8 AND #3 (277)
18. #16 AND #3 (196)
19. #18 OR #17 (324)

### Inside Conferences: Dialog (File 65)

The Inside Conferences search covered the date range 1990 to date. The search was carried out on 24 November 2005 and identified 121 records.

Records on the Inside Conferences databases are very brief and abstracts are not included. The 'infection' terms in the strategy were removed for this search, to broaden it, so that potentially relevant papers might be identified.

1. s vancomycin or vancocin or lyphocin or vancoled or vancor or teicoplanin or teichomycin? or targocid or glycopeptide? (506)
2. s ((antibiotic? or anti(w)microbial? or antimicrobial? or anti(w)bacterial? or antibacterial? or anti(w)mycobacterial? or antimycobacterial? or bacteriocidal or bacteriocide?)(2n)(prophyla? or premedicat? or pre(w)medicat? or therapeutic?)) (199)
3. s surgery or surgical or operat? or preoperat? or pre(w)operat? or intraoperat? or intra(w)operat? or perioperat? or peri(w)operat? or prosth? or implant? or bypass or graft? or resection or dissect? or incision? or biopsy or biopsies or amputat? or hysterectom? or abortion? (157507)
4. s ((hip or hips or knee or knees or joint?)(w)(replac? or arthroplast?)) (2974)
5. s c(w)section? or caesarean? or ceasarean? or cesarean? or caesarian? or ceasarian? or cesarian? (593)
6. s s3:s5 (160417)
7. s s1 and s6 (22)
8. s s2 and s6 (99)
9. s s7 or s8 (121)
10. s s9/1990:2005 (121)

### National Research Register: Internet (<http://www.update-software.com/national>)

Issue 2005/3 of the National Research Register was searched to identify ongoing and recently completed research projects. The search was

carried out on 22 September 2005 and identified 76 projects.

1. VANCOMYCIN single term (MeSH) (26)
2. vancomycin (61)
3. vancocin (0)
4. lyphocin (0)
5. vancoled (0)
6. vancor (0)
7. TEICOPLANIN single term (MeSH) (13)
8. teicoplanin (29)
9. teichomycin\* (0)
10. targocid (0)
11. GLYCOPEPTIDES explode tree 1 (MeSH) (78)
12. ANTIBIOTICS GLYCOPEPTIDE single term (MeSH) (22)
13. glycopeptide\* (39)
14. ANTIBIOTIC PROPHYLAXIS single term (MeSH) (46)
15. PREMEDICATION single term (MeSH) (8)
16. ((antibiotic\* near prophyla\*) or (antibiotic\* near premedicat\*) or (antibiotic\* near (pre next medicat\*)) or antibiotic\* near therapeutic\*)) (519)
17. (((anti next microbial\*) near prophyla\*) or ((anti next microbial\*) near premedicat\*) or ((anti next microbial\*) near (pre next medicat\*)) or ((anti next microbial\*) near therapeutic\*) or (antimicrobial\* near prophyla\*) or (antimicrobial\* near premedicat\*) or (antimicrobial\* near (pre next medicat\*)) or (antimicrobial\* near therapeutic\*)) (16)
18. (((anti next bacterial\*) near prophyla\*) or ((anti next bacterial\*) near premedicat\*) or ((anti next bacterial\*) near (pre next medicat\*)) or ((anti next bacterial\*) near therapeutic\*) or (antibacterial\* near prophyla\*) or (antibacterial\* near premedicat\*) or (antibacterial\* near (pre next medicat\*)) or (antibacterial\* near therapeutic\*)) (32)
19. (((anti next mycobacterial\*) near prophyla\*) or ((anti next mycobacterial\*) near premedicat\*) or ((anti next mycobacterial\*) near (pre next medicat\*)) or ((anti next mycobacterial\*) near therapeutic\*) or (antimycobacterial\* near prophyla\*) or (antimycobacterial\* near premedicat\*) or (antimycobacterial\* near (pre next medicat\*)) or (antimycobacterial\* near therapeutic\*)) (0)
20. ((bacteriocidal near prophyla\*) or (bacteriocidal near premedicat\*) or (bacteriocidal near (pre next medicat\*)) or (bacteriocidal near therapeutic\*) or (bacteriocide\* near prophyla\*) or



- (bactericide\* near premedicat\*) or (bactericide\* near (pre next medicat\*)) or (bactericide\* near therapeutic\*) (0)
21. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20) (673)
  22. BACTERIAL INFECTIONS single term (MeSH) (158)
  23. ((bacteri\* near infect\*) or (wound\* near infect\*) or (tissue\* near infect\*) or (prosth\* near infect\*) or (bacteri\* near contam\*) or (wound\* near contam\*) or (tissue\* near contam\*) or (prosth\* near contam\*)) (926)
  24. SOFT TISSUE INFECTIONS single term (MeSH) (2)
  25. PROSTHESIS-RELATED INFECTIONS single term (MeSH) (12)
  26. SEPSIS single term (MeSH) (194)
  27. sepsis (580)
  28. (hospital\* near infect\*) (1049)
  29. (mrsa or visa or gisa or vrsa) (159)
  30. ((methicillin\* next resist\*) or (meticillin\* next resist\*) or (methycillin\* next resist\*)) (126)
  31. STAPHYLOCOCCACEAE single term (MeSH) (0)
  32. STAPHYLOCOCCUS explode tree 1 (MeSH) (96)
  33. staphylococc\* (241)
  34. (micrococcus next pyogenes) (0)
  35. STAPHYLOCOCCAL INFECTIONS explode tree 1 (MeSH) (119)
  36. GRAM-POSITIVE BACTERIA single term (MeSH) (5)
  37. GRAM-POSITIVE BACTERIAL INFECTIONS single term (MeSH) (24)
  38. (gram next positive next bacteri\*) (36)
  39. GRAM-POSITIVE COCCI single term (MeSH) (1)
  40. (gram next positive next cocci) (6)
  41. METHICILLIN RESISTANCE single term (MeSH) (88)
  42. METHICILLIN single term (MeSH) (4)
  43. PENICILLIN RESISTANCE single term (MeSH) (0)
  44. DRUG RESISTANCE MICROBIAL single term (MeSH) (155)
  45. (#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44) (2734)
  46. SURGICAL PROCEDURES OPERATIVE explode tree 1 (MeSH) (8738)
  47. (surgery or surgical or operat\*) (19869)
  48. (preoperat\* or (pre next operat\*)) (1607)
  49. (intraoperat\* or (intra next operat\*)) (483)
  50. (perioperat\* or (peri next operat\*)) (468)
  51. PROSTHESES AND IMPLANTS explode tree 1 (MeSH) (1047)
  52. (prosth\* or implant\*) (1924)
  53. (bypass or graft\*) (2140)
  54. (resection or dissect\* or incision\*) (1720)
  55. (biopsy or biopsies) (2457)
  56. amputat\* (335)
  57. ((hip\* next replac\*) or (knee\* next replac\*) or (joint\* next replac\*) or (arthroplast\* next replac\*) or (hip\* next arthroplast\*) or (knee\* next arthroplast\*) or (joint\* next arthroplast\*) or (arthroplast\* next arthroplast\*)) (1046)
  58. ((c next section\*) or caesarean\* or ceasarean\* or cesarean\* or caesarian\* or cesarian\* or cesarian\*) (540)
  59. hysterectom\* (358)
  60. abortion\* (298)
  61. (#46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60) (616)
  62. SURGICAL WOUND INFECTION single term (MeSH) (72)
  63. ((surgery near infect\*) or (surgical near infect\*) or (surgery near contam\*) or (surgical near contam\*)) (260)
  64. ((incision\* near infect\*) or (incision\* near contam\*)) (6)
  65. ((postoperat\* near infect\*) or ((post next operat\*) near infect\*)) (171)
  66. (#62 or #63 or #64 or #65) (366)
  67. (#21 and #45 and #61) (63)
  68. (#21 and #66) (48)
  69. (#67 or #68) (76)
- metaRegister of Controlled Trials: Current Controlled Trials (<http://controlled-trials.com/mrct>)**
- The mRCT was searched on the Internet on 23 September 2005. The results were scanned for relevance and four potentially relevant trials were identified.
- The search interface for the mRCT allows only very simple searching. The following terms were entered line-by-line:
- vancomycin OR vancocin OR lyphocin OR vancoled OR vancor OR teicoplanin OR teichomycin% OR targocid OR glycopeptide% (25)
  - "antibiotic prophylaxis" OR "anti-microbial prophylaxis" OR "antimicrobial prophylaxis" OR "anti-bacterial prophylaxis" OR "antibacterial prophylaxis" (20)
  - "surgical wound infection" OR "surgical wound infections" or "surgical infection" OR "surgical

infections" OR "surgical contamination" OR "surgical contaminations" (1)

- "postoperative wound infection" OR "post-operative wound infection" OR "postoperative wound infections" OR "post-operative wound infections" (1)
- "postoperative infection" OR "post-operative infection" OR "postoperative infections" OR "post-operative infections" (4).

### **National Technical Information Service: Internet (<http://www.ntis.gov/search/index.asp?loc=3-0-0>)**

The NTIS was searched on the Internet on 23 September 2005. The results were scanned for relevance and one potentially relevant record was identified.

The search interface for the NTIS allows only very simple searching. The following terms were entered line-by-line:

- vancomycin OR vancocin OR lyphocin OR vancoled OR vancor OR teicoplanin OR teichomycin OR teichomycins OR targocid OR glycopeptide OR glycopeptides (30)
- "antibiotic prophylaxis" OR "anti-microbial prophylaxis" OR "antimicrobial prophylaxis" OR "anti-bacterial prophylaxis" OR "antibacterial prophylaxis" (7)
- "surgical wound infection" OR "surgical wound infections" OR "surgical infection" OR "surgical infections" OR "surgical contamination" OR "surgical contaminations" (4)
- "postoperative wound infection" OR "post-operative wound infection" OR "postoperative wound infections" OR "post-operative wound infections" (0)
- "postoperative infection" OR "post-operative infection" OR "postoperative infections" OR "post-operative infections" (0).

### **Internet**

The Internet searching was carried out on 1 December 2005 through the specialist search engine OMNI and the meta-search engine Copernic.

#### **OMNI: Internet (<http://www.omni.ac.uk>)**

The web resources identified through OMNI were scanned and eight potentially relevant web pages were downloaded for consideration by the reviewers.

The search interface for OMNI allows only simple searching. The following terms were entered line-by-line:

- vancomycin OR vancocin OR lyphocin OR vancoled OR vancor OR teicoplanin OR teichomycin OR teichomycins OR targocid OR glycopeptide OR glycopeptides (1)
- "antibiotic prophylaxis" (8)
- "anti-microbial prophylaxis" (0)
- "antimicrobial prophylaxis" (2)
- "anti-bacterial prophylaxis" (0)
- "antibacterial prophylaxis" (0)
- "surgical wound infection" (3)
- "surgical wound infections" (0)
- "surgical infection" (0)
- "surgical infections" (0)
- "surgical contamination" (0)
- "surgical contaminations" (0)
- "postoperative wound infection" (0)
- "post-operative wound infection" (0)
- "postoperative wound infections" (0)
- "post-operative wound infections" (0)
- "postoperative infection" (0)
- "post-operative infection" (0)
- "postoperative infections" (0)
- "post-operative infections" (0).

#### **Copernic: Internet (<http://www.copernic.com>)**

The web resources identified through Copernic were scanned and 15 potentially relevant web pages were downloaded for consideration by the reviewers.

The search interface for Copernic allows only simple searching. The following terms were entered line-by-line:

- vancomycin vancocin lyphocin vancoled vancor teicoplanin teichomycin teichomycins targocid glycopeptide glycopeptides [Any word] (41)
- "antibiotic prophylaxis" surgery [All words] (36)
- "anti-microbial prophylaxis" surgery [All words] (33)
- "antimicrobial prophylaxis" surgery [All words] (38)
- "anti-bacterial prophylaxis" surgery [All words] (18)
- "antibacterial prophylaxis" surgery [All words] (45)
- surgical wound infection [Exact phrase] (37)
- surgical wound infections [Exact phrase] (42)
- surgical infection [Exact phrase] (37)
- surgical infections [Exact phrase] (40)
- surgical contamination [Exact phrase] (41)
- postoperative wound infection [Exact phrase] (46)
- post-operative wound infection [Exact phrase] (43)
- postoperative wound infections [Exact phrase] (41)

- post-operative wound infections [Exact phrase] (38)
- postoperative infection [Exact phrase] (41)
- post-operative infection [Exact phrase] (47)
- postoperative infections [Exact phrase] (38)
- post-operative infections [Exact phrase] (38).

## Economic evaluations

Economic evaluations were identified through the strategies run in the resources listed above, along with further searches of NHS EED, HEED and IDEAS. The strategies used to identify economic evaluations in these databases are listed below.

### NHS EED: Internal CRD Database

The NHS EED search was carried out on 18 October 2005, using the CRD's internal search interface. The search identified 140 records.

Date limits were not set within the search as pre-1990 records were deleted within the endnote library.

1. S vancomycin or vancocin or lyphocin or vancoled or vancor or teicoplanin or teichomycin\$ or targocid or glycopeptide\$ (88)
2. S antibiotic\$(2w)(prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$) (88)
3. S ((anti-microbial\$ or antimicrobial\$(2w)(prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)) (8)
4. S ((anti-bacterial\$ or antibacterial\$(2w)(prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)) (2)
5. S ((anti-mycobacterial\$ or antimycobacterial\$(2w)(prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)) (0)
6. S ((bacteriocidal or bactericide\$(2w)(prophyla\$ or premedicat\$ or pre-medicat\$ or therapeutic\$)) (0)
7. s S1 or s2 or s3 or s4 or s5 or s6 (140)

### HEED: CD-ROM (issue October 2005)

The HEED search was carried out on 19 October 2005 and identified 244 records.

Date limits were not set within the search as pre-1990 records were deleted within the endnote library.

1. AX=vancomycin OR vancocin OR lyphocin OR vancoled OR vancOR OR teicoplanin OR teichomycin\* OR targocid OR glycopeptide\* (144)

2. AX='antibiotic prophylaxis' within 2 OR 'antibiotic premedication' within 2 OR 'antibiotic pre-medication' within 2 OR 'antibiotic therapeutic' within 2 (78)
3. AX='antibiotics prophylaxis' within 2 OR 'antibiotics premedication' within 2 OR 'antibiotics pre-medication' within 2 OR 'antibiotics therapeutic' within 2 (5)
4. AX='anti-microbial prophylaxis' within 2 OR 'anti-microbial premedication' within 2 OR 'anti-microbial pre-medication' within 2 OR 'anti-microbial therapeutic' within 2 (0)
5. AX='anti-microbials prophylaxis' within 2 OR 'anti-microbials premedication' within 2 OR 'anti-microbials pre-medication' within 2 OR 'anti-microbials therapeutic' within 2 (0)
6. AX='antimicrobial prophylaxis' within 2 OR 'antimicrobial premedication' within 2 OR 'antimicrobial pre-medication' within 2 OR 'antimicrobial therapeutic' within 2 (27)
7. AX='antimicrobials prophylaxis' within 2 OR 'antimicrobials premedication' within 2 OR 'antimicrobials pre-medication' within 2 OR 'antimicrobials therapeutic' within 2 (1)
8. AX='anti-bacterial prophylaxis' within 2 OR 'anti-bacterial premedication' within 2 OR 'anti-bacterial pre-medication' within 2 OR 'anti-bacterial therapeutic' within 2 (1)
9. AX='anti-bacterials prophylaxis' within 2 OR 'anti-bacterials premedication' within 2 OR 'anti-bacterials pre-medication' within 2 OR 'anti-bacterials therapeutic' within 2 (0)
10. AX='antibacterial prophylaxis' within 2 OR 'antibacterial premedication' within 2 OR 'antibacterial pre-medication' within 2 OR 'antibacterial therapeutic' within 2 (2)
11. AX='antibacterials prophylaxis' within 2 OR 'antibacterials premedication' within 2 OR 'antibacterials pre-medication' within 2 OR 'antibacterials therapeutic' within 2 (0)
12. AX='anti-mycobacterial prophylaxis' within 2 OR 'anti-mycobacterial premedication' within 2 OR 'anti-mycobacterial pre-medication' within 2 OR 'anti-mycobacterial therapeutic' within 2 (0)
13. AX='anti-mycobacterials prophylaxis' within 2 OR 'anti-mycobacterials premedication' within 2 OR 'anti-mycobacterials pre-medication' within 2 OR 'anti-mycobacterials therapeutic' within 2 (0)
14. AX='antimycobacterial prophylaxis' within 2 OR 'antimycobacterial premedication' within 2 OR 'antimycobacterial pre-medication' within 2 OR 'antimycobacterial therapeutic' within 2 (0)
15. AX='antimycobacterials prophylaxis' within 2 OR 'antimycobacterials premedication' within

- 2 OR 'antimycobacterials pre-medication' within 2 OR 'antimycobacterials therapeutic' within 2 (0)
16. AX='bacteriocidal prophylaxis' within 2 OR 'bacteriocidal premedication' within 2 OR 'bacteriocidal pre-medication' within 2 OR 'bacteriocidal therapeutic' within 2 (0)
17. AX='bacteriocide prophylaxis' within 2 OR 'bacteriocide premedication' within 2 OR 'bacteriocide pre-medication' within 2 OR 'bacteriocide therapeutic' within 2 (0)
18. AX='bacteriocides prophylaxis' within 2 OR 'bacteriocides premedication' within 2 OR 'bacteriocides pre-medication' within 2 OR 'bacteriocides therapeutic' within 2 (0)
19. CS=1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (244)

### IDEAS: Internet (<http://ideas.repec.org>)

The IDEAS search was carried out on 20 October 2005. No relevant papers were identified.

The search interface for IDEAS allows only simple searching. The following terms were entered line-by-line:

- vancomycin or vancocin or lyphocin or vancoled or vancor or teicoplanin or teichomycin\* or targocid or glycopeptide\* (0)
- antibiotic\* and (prophyla\* or premedicat\* or pre-medicat\* or therapeutic\*) (0)
- anti-microbial\* and (prophyla\* or premedicat\* or pre-medicat\* or therapeutic\*) (0)
- antimicrobial\* and (prophyla\* or premedicat\* or pre-medicat\* or therapeutic\*) (0)
- anti-bacterial\* and (prophyla\* or premedicat\* or pre-medicat\* or therapeutic\*) (0)
- antibacterial\* and (prophyla\* or premedicat\* or pre-medicat\* or therapeutic\*) (0)
- anti-mycobacterial\* and (prophyla\* or premedicat\* or pre-medicat\* or therapeutic\*) (0)
- antimycobacterial\* and (prophyla\* or premedicat\* or pre-medicat\* or therapeutic\*) (0)
- bacteriocidal and (prophyla\* or premedicat\* or pre-medicat\* or therapeutic\*) (0)
- bacteriocide\* and (prophyla\* or premedicat\* or pre-medicat\* or therapeutic\*) (0)

### Economic model

Restricted searches to inform the economic model were undertaken.

Searches were performed on NHS EED via the CRD's internal search interface, to identify:

- economic evaluations of glycopeptides versus non-glycopeptides
- economic evaluations on prophylaxis for surgery
- economic evaluations that assess the prevalence of surgical site infections
- economic evaluations of antimicrobial resistance.

Searches were performed on MEDLINE via Ovid (<http://gateway.ovid.com/athens>), to identify:

- papers on epidemiological modelling
- papers on decision analysis and antibiotics.

Searches were performed on MEDLINE and EMBASE via Ovid (<http://gateway.ovid.com/athens>), to identify:

- papers on treatments used when antimicrobial resistance is a problem
- conceptual papers on evaluating the impact of MRSA/antimicrobial resistance.

Searches were performed on MEDLINE, EMBASE and CINAHL via Ovid (<http://gateway.ovid.com/athens>) and NHS EED via the CRD's internal search interface, to identify:

- papers on modelling resistance.

Full details of the strategies used to inform the economic model are available from the CRD (tel. 01904 321846; email [crd-info@york.ac.uk](mailto:crd-info@york.ac.uk)).

## Appendix 2

### Quality assessment checklists

#### Effectiveness review

1. Was the assignment to treatment groups really random?

*Adequate approaches to sequence generation:*

- Computer-generated random numbers
- Random numbers tables.

*Inadequate approaches to sequence generation:*

- Use of alternation, case record numbers, birth dates or week days.

2. Method of randomisation.

3. Was the allocation of treatment concealed?

*Adequate approaches to concealment of randomisation:*

- Centralised or pharmacy-controlled randomisation
- Serially numbered identical containers
- On-site computer based system with a randomisation sequence that is not readable until allocation
- Other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients.

*Inadequate approaches to concealment of randomisation:*

- Use of alternation, case record numbers, birth dates or week days
- Open random numbers lists
- Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation).

4. Were the groups similar at baseline?
5. Were eligibility criteria specified?
6. Were outcome assessors blinded to treatment?
7. Was the patient blinded to treatment?
8. Were analyses on an intention-to-treat basis?
9. Was there an appropriate sample size calculation?
10. Were withdrawals reported?

#### Cost-effectiveness review

Studies of cost-effectiveness will be assessed using the following criteria, which is an updated version of the checklist developed by Drummond and colleagues:<sup>34</sup>

#### Study question

1. Costs and effects examined.

2. Alternatives compared.
3. The viewpoint(s)/perspective of the analysis is clearly stated (*e.g. NHS, society*).

#### Selection of alternatives

4. All relevant alternatives are compared (*including do nothing if applicable*).
5. The alternatives being compared are clearly described (*who did what, to whom, where and how often*).
6. The rationale for choosing the alternative programmes or interventions compared is stated.

#### Form of evaluation

7. The choice of form of economic evaluation is justified in relation to the questions addressed.
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?

#### Effectiveness data

9. The source(s) of effectiveness estimates used are stated (*e.g. single study, selection of studies, systematic review, expert opinion*).
10. Effectiveness data from RCT or review of RCTs.
11. Potential biases identified (especially if data not from RCTs).
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies).

#### Costs

13. All the important and relevant resource use included.
14. All the important and relevant resource use measured accurately (with methodology).
15. Appropriate unit costs estimated (with methodology).
16. Unit costs reported separately from resource use data.
17. Productivity costs treated separately from other costs.
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.

**Benefit measurement and valuation**

19. The primary outcome measure(s) for the economic evaluation are clearly stated (*cases detected, life-years, QALYs, etc.*).
20. Methods to value health states and other benefits are stated (*e.g. time trade-off*).
21. Details of the individuals from whom valuations were obtained are given (*patients, members of the public, healthcare professionals, etc.*).

**Decision modelling**

22. Details of any decision model used are given (*e.g. decision tree, Markov model*).
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified.
24. All model outputs described adequately.

**Discounting**

25. Discount rate used for both costs and benefits.
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?

**Allowance for uncertainty****Stochastic analysis of patient-level data**

27. Details of statistical tests and CIs are given for stochastic data.
28. Uncertainty around cost-effectiveness expressed (*e.g. CI around ICER, cost-effectiveness acceptability curves*).
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (*e.g. unit costs, discount rates*) and analytic decisions (*e.g. methods to handle missing data*).

**Stochastic analysis of decision models**

30. Are all appropriate input parameters included with uncertainty?
31. Is second-order uncertainty (uncertainty in means) included rather than first-order uncertainty (uncertainty between patients)?
32. Are the probability distributions adequately detailed and appropriate?
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (*e.g. unit costs, discount rates*) and analytic decisions (*e.g. methods to handle missing data*).

**Deterministic analysis**

34. The approach to sensitivity analysis is given (*e.g. univariate, threshold analysis*).
35. The choice of variables for sensitivity analysis is justified.
36. The ranges over which the variables are varied are stated.

**Presentation of results**

37. Incremental analysis is reported using appropriate decision rules.
38. Major outcomes are presented in a disaggregated as well as an aggregated form.
39. Applicable to the NHS setting.

All items will be graded as either ✓ = yes (item adequately addressed), ✗ = no (item not adequately addressed), ? = unclear or not enough information, NA = not applicable or NS = not stated.

## Appendix 3

### Studies excluded from the effectiveness review

Study	Reason for exclusion
Antrum, 1990 <sup>113</sup>	Interim analysis of Kester, 1999 <sup>23</sup>
Antrum, 1992 <sup>114</sup>	Interim analysis of Kester, 1999 <sup>23</sup>
Barlas, 1993 <sup>115</sup>	CCT but not assessing a glycopeptide (full paper was ordered as no abstract was available)
Bayston, 1990 <sup>116</sup>	Not adult participants only
Bell, 1990 <sup>117</sup>	Not a CCT (case series: full paper was ordered as no abstract was available)
Brooks, 2002 <sup>118</sup>	Not a CCT (prospective cohort study)
Bucknell, 2000 <sup>119</sup>	CCT but not assessing a glycopeptide (only MRSA high-risk patients received a glycopeptide)
Cone, 2004 <sup>120</sup>	Duplicate of Mastronardi, 2004 <sup>121</sup>
Dazzi, 1994 <sup>122</sup>	Comparator not an alternative antibiotic regimen
de Lalla, 2000 <sup>123</sup>	Comparator not an alternative antibiotic regimen
de Lalla, 2001 <sup>124</sup>	Discussion paper (full paper was ordered as no abstract was available)
De Lucas-Villarrubia, 2004 <sup>125</sup>	Not a CCT (prospective cohort study)
Exner, 1992 <sup>126</sup>	Not a CCT (prospective cohort study)
Ferro, 1997 <sup>127</sup>	Comparator not an alternative antibiotic regimen
Feys, 1997 <sup>128</sup>	Comparator not an alternative antibiotic regimen
Fontanesi, 1991 <sup>129</sup>	Discussion paper (full paper was ordered as no abstract was available)
Franchelli, 1993 <sup>130</sup>	Comparator not an alternative antibiotic regimen
Friberg, 1990 <sup>131</sup>	Not a CCT (case reports: full paper was ordered as no abstract was available)
Gadallah, 2000 <sup>132</sup>	Not adult participants only. Primary outcome was peritonitis, SSIs were excluded from the analysis
Haines, 1993 <sup>133</sup>	Letter
Isringhaus, 1992 <sup>134</sup>	Not a CCT (pharmacokinetic study: all patients received same dose of glycopeptide)
Karran, 1992 <sup>135</sup>	Comparator not an alternative antibiotic regimen
Lazzarini, 2001 <sup>136</sup>	Not a CCT (prospective cohort)
Lazzarini, 2003 <sup>137</sup>	Does not report a primary outcome (primary outcome is blood drug concentration)
Mastronardi, 2004 <sup>121</sup>	Not a CCT (retrospective cohort)
Mendivil Soto, 2001 <sup>138</sup>	Does not report a primary outcome
Mini, 1999 <sup>139</sup>	Discussion paper (full paper was ordered as no abstract was available)
Nehrer, 1998 <sup>140</sup>	Not a CCT (prospective cohort)
Niederhäuser, 1997 <sup>141</sup>	Prophylaxis not started before or during surgery (patients were randomised after surgery)
Pear, 1998 <sup>142</sup>	Not a CCT (prospective cohort)
Periti, 1992 <sup>143</sup>	Interim analysis of Periti, 1999 <sup>24</sup>
Rao, 2004 <sup>144</sup>	Not a CCT (prospective cohort)
Renz, 1999 <sup>145</sup>	Does not report a primary outcome and glycopeptide vs an alternative antibiotic regimen not main comparison
Saginur, 1995 <sup>146</sup>	Abstract of Saginur, 2000 <sup>18</sup>
Santini, 1997 <sup>147</sup>	Discussion paper (full paper was ordered as no abstract was available)
Sassone, 1991 <sup>148</sup>	Not a CCT (prospective cohort)
Seppala, 2004 <sup>149</sup>	Not a CCT (prospective cohort)
Shimada, 1995 <sup>150</sup>	Comparator not an alternative antibiotic regimen
Skinner, 2001 <sup>151</sup>	Not a CCT(case report: full paper was ordered as no abstract was available)
Sobaci, 2003 <sup>152</sup>	Does not report a primary outcome
Steer, 1997 <sup>153</sup>	Comparator not an alternative antibiotic regimen
Tinelli, 1994 <sup>154</sup>	Not a CCT (epidemiological study)
Tinelli, 1995 <sup>155</sup>	Not a CCT (epidemiological study)
Trenholme, 1991 <sup>156</sup>	Abstract only, not enough information reported to extract outcome data
Wilson, 1990 <sup>157</sup>	Discussion paper: reports results of two trials but both published pre-1990
Zibari, 1997 <sup>158</sup>	Comparator not an alternative antibiotic regimen





## **Appendix 4**

### Data extraction tables: effectiveness review

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
Caprioli, 1995 <sup>14</sup> Italy Setting: unclear Specialty: orthopaedic	<i>Inclusion criteria:</i> Undergoing hip or elbow prosthetic surgery Number of patients: 174 MRSA prevalence: not reported	<b>Cefamandole</b> Dosage: 2 g 1 h before surgery, then 1 g at end of surgery Route: i.v. Additional drugs: none <b>Vancomycin</b> Dosage: 1 g 2 h before surgery Route: i.v. Additional drugs: plus gentamicin 80 mg	<b>Cefamandole</b> Number evaluated: 91 <b>Vancomycin</b> Number evaluated: 83	<b>Cefamandole</b> SSI: wound infection 4/91 Infection (other): fever 50/91; pleuritis 1/91; pneumonia 1/91; sepsis 1/91; urinary tract 6/91 <b>Vancomycin</b> SSI: wound infection 2/83 Infection (other): fever 44/83; pleuritis 1/83; pneumonia 1/83; sepsis 1/83; urinary tract 5/83 Adverse events: <b>Cefamandole</b> No AEs reported <b>Vancomycin</b> No AEs reported	Conference abstract, many study details missing. Authors state groups were comparable for sex, age, risk factors and type of surgery. No major AEs were observed in either group. In wound infections and sepsis 8 bacteria ( <i>S. aureus</i> ) were isolated in the cefamandole group and 4 (no <i>S. aureus</i> ) in the vancomycin + gentamicin group <i>Quality assessment</i> Not enough information to assess quality <i>Conclusion</i> The two regimens seem to be comparable in effectiveness
Codina, 2000 <sup>13</sup> Spain Setting: teaching Hospital Specialty: cardiac	<i>Inclusion criteria:</i> Undergoing elective cardiac surgery <i>Exclusion criteria:</i> Allergy to glycopeptides or netilmicin; active infection; treatment with antibiotic in 5 days prior to surgery; renal insufficiency Definition of infection: postoperative infections defined by CDC criteria Number of patients: 500 MRSA prevalence: not reported	<b>Teicoplanin</b> Dosage: 400 mg at induction of anaesthesia Route: i.v. Additional drugs: plus netilmicin 150 mg and vancomycin placebo. Valve replacement patients received a second dose (200 mg teicoplanin) at the end of extracorporeal circulation <b>Vancomycin</b> Dosage: 1 g at induction of anaesthesia Route: i.v. Additional drugs: plus netilmicin 150 mg and teicoplanin placebo. Valve replacement patients received a second dose at the end of extracorporeal circulation	<b>Teicoplanin</b> Number evaluated: 250 % male: 67 Age (years): 64 ± 11 <b>Vancomycin</b> Number evaluated: 250 % male: 67 Age (years): 64 ± 12 <i>Surgery details:</i> <b>Teicoplanin</b> CABG Valve replacement 135/250 115/250 <b>Vancomycin</b> CABG Valve replacement 132/250 118/250	<b>Teicoplanin</b> SSI: any infection 22/250 <b>Vancomycin</b> SSI: any infection 21/250 Adverse events: <b>Teicoplanin</b> Patients with an AE (first dose): 4/250; hypotension: 1/250. Patients with an AE (VR second dose): 1/115 <b>Vancomycin</b> Patients with an AE (first dose): 51/250; hypotension: 1/250. Patients with an AE (VR second dose): 6/118	Sample size calculation based on AEs rather than efficacy. The paper reports an ancillary cost minimisation analysis of an RCT; the conclusions relate to the costs of treatment in different settings. No further details of infections are reported <i>Quality assessment</i> <sup>d</sup> 1. Yes 2. Computer program (Epistat) 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Unclear

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
de Lalla, 1993 <sup>27</sup> Italy Setting: unclear Specialty: orthopaedic	<b>Inclusion criteria:</b> Undergoing elective monolateral or bilateral TKR; not stated as inclusion criteria but all participants had normal kidney and liver function and no antimicrobial treatment in week prior to surgery Number of patients: 24 Follow-up: immediately after operation with longer term follow-up 12–26 months MRSA prevalence: not reported Surgical procedures: tourniquet inflated to 400 mmHg immediately before surgery and kept in place throughout	<b>Teicoplanin (regional)</b> Dosage: 400 mg in foot vein of operated leg(s) straight after inflation of tourniquet Route: i.v. <b>Teicoplanin (systemic)</b> Dosage: 800 mg in forearm vein 2.5 h before surgery Route: i.v.	<b>Teicoplanin (regional)</b> Number evaluated: 13 % male: 8 Age (years): 68.5 ± 5.6 <b>Teicoplanin (systemic)</b> Number evaluated: 11 % male: 27 Age (years): 70 ± 6 <i>Surgery details:</i> <b>Teicoplanin (regional)</b> Bilateral TKR 5/13 Monolateral TKR 8/13 <b>Teicoplanin (systemic)</b> Bilateral TKR 5/11 Monolateral TKR 6/11	<b>Teicoplanin (regional)</b> No SSI reported either postoperatively or at 12 months <b>Teicoplanin (systemic)</b> No SSI reported either postoperatively or at 12 months <i>Adverse events:</i> <b>Teicoplanin (regional)</b> No AEs reported <b>Teicoplanin (systemic)</b> No AEs reported	Primarily a pharmacokinetic study but reports absence of SSIs and AEs. Mean duration of surgery 113 (SD 30) minutes overall. Mean serum teicoplanin concentrations were 2–10 times higher after regional compared with systemic prophylaxis (full details reported). Intraoperative levels obtained by systemic prophylaxis could be inadequate to inhibit some strains of CNS <i>Quality assessment</i> 1. Unclear 2. Not reported 3. Unclear 4. Yes 5. Unclear 6. Unclear 7. Unclear 8. Unclear 9. Unclear 10. Unclear <i>Conclusion</i> Regional prophylaxis seems to be a safe technique and provides higher antibiotic concentrations than systemic prophylaxis

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
Finkelstein, 2002 <sup>17</sup> Israel Setting: teaching hospital Specialty: cardiac	<b>Inclusion criteria:</b> 18 years or over; undergoing cardiac surgery requiring sternotomy <b>Exclusion criteria:</b> Presence of active infection; use of antibiotics in previous 2 weeks; previous cardiac surgery with sternotomy within 1 year of trial enrollment <b>Definition of infection:</b> CDC definitions: superficial (involving only skin and subcutaneous tissue); deep incisional (involving deep soft tissues of the incision); mediastinitis (specific organ-space infection); sternal osteomyelitis (specific organ-space infection with persistent purulent drainage from the sternotomy); pericarditis and endocarditis (both specific organ-space infections) Number of patients: 1032 Follow-up: daily during hospitalisation, 1 week and 4 weeks after discharge. At least 1 year for patients with a cardiac implant Surgical site preparation: showered with 7.5% povidone-iodine scrub; hair removed from surgical site with hair-removing cream; in theatre all sites scrubbed with	<b>Cefazolin</b> Dosage: 1 g at induction, then 1 g at 8 and 16 h Route: i.v. Other details: dose given over 20–30 minutes. 94.5% of patients received drug within 2 h of the first incision <b>Vancomycin</b> Dosage: 1 g at induction, then 1 g after 12 h Route: i.v. Other details: dose given over 1 h. 92.4% of patients received drug within 2 h of the first incision	<b>Cefazolin</b> Number evaluated: 433 % male: 72 Age (years): 61.2 ± 12.8 <b>Risk factors:</b> ASA score of ≥ 3 n = 390 NINISS risk score 0 n = 35 NINISS risk score 1 n = 289 NINISS risk score 2 n = 109 <b>Vancomycin</b> Number evaluated: 452 % male: 72 Age (years): 60.9 ± 12.2 <b>Risk factors:</b> ASA score of ≥ 3 n = 413 NINISS risk score 0 n = 33 NINISS risk score 1 n = 291 NINISS risk score 2 n = 128 <b>Surgery details:</b> <b>Cefazolin</b> CABG (chest and leg) 31/4/433 CABG (chest only) 12/433 CABG and other cardiac operation 26/433 Cardiac implant 70/433 Other cardiac operation 81/433 Duration of surgery (minutes) 273.7 ± 70.9 <b>Vancomycin</b> CABG (chest and leg) 329/452 CABG (chest only) 10/452 CABG and other cardiac operation 32/452 Cardiac implant 90/452 Other cardiac operation 81/452 Duration of surgery (minutes) 284.8 ± 74	<b>Cefazolin</b> SSI (30 days): any SSI: 39/433; deep incisional chest: 5/433; deep incisional donor site: 2/433; organ-space: 12/433; superficial chest: 10/433; superficial donor site: 10/433 MRSA/bacteria: SSI: Gram-positive (total): 26/433; MRSA: 7/433; MSSA: 5/433; MR-CNS: 8/433; MS-CNS: 1/433; enterococci: 5/433 Gram-negative: 20/433 Bloodstream: Gram-positive (total): 10/443; MRSA: 4/443; MSSA: 2/433; MR-CNS: 2/443; MS-CNS: 0/433 Gram-negative: 7/433 Infection (other): bloodstream: 18/433 Mortality: 14/433 Duration of post-operative stay (days): 9.3 ± 11 <b>Vancomycin</b> SSI (30 days): any SSI: 43/452; deep incisional chest: 10/452; deep incisional donor site: 2/452; organ-space: 6/452; superficial chest: 18/452; superficial donor site: 7/452 MRSA/bacteria: SSI: Gram-positive (total): 26/452; MRSA: 2/452; MSSA: 10/452; MR-CNS: 6/452; MS-CNS: 7/452; enterococci: 1/452	Study concludes that there was no clear advantage of vancomycin over cefazolin in reducing SSI rates in cardiac surgery at their institution, where the prevalence of MRSA infections was high. Bacteriological results also reported for bloodstream infections although these only occurred in patients with chest infections. AEs were not reported <b>Quality assessment</b> 1. No 2. Alternation using patient's national identification number 3. No 4. Yes 5. Yes 6. Unclear 7. Unclear 8. Unclear 9. Yes 10. Yes

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
	<p>povidone-iodine soap and painted with 10% povidone-iodine-ethanol tincture; sternotomy site covered with iodine membrane</p> <p>MRSA prevalence: 3 and 2.6 new cases of MRSA infection or colonisation per 100 admissions in the cardiac surgery ward in 1995 and 1996 respectively (classed as high prevalence)</p> <p>Surgical procedures: skin wounds closed with stainless steel clips. All procedures performed by the same team of four surgeons</p>			<p>Gram-negative: 21/452</p> <p>Bloodstream: Gram-positive (total): 12/452; MRSA: 2/452; MSSA: 6/452; MR-CNS: 2/452; MS-CNS: 1/452</p> <p>Gram-negative: 11/452</p> <p>Infection (other): bloodstream: 20/452</p> <p>Mortality: 13/452</p> <p>Duration of post-operative stay (days): 8.7 ± 8</p>	
Kester, 1999 <sup>23</sup> UK	<p><i>Inclusion criteria:</i> Vascular surgical procedure with risk of postoperative wound infection; at least 14 years old at study entry</p> <p><i>Exclusion criteria:</i> Antimicrobial treatment within 12 h of study entry; severe hepatic or renal impairment; allergy to study drugs; pregnancy or lactation; prophylactic use of non-study antibiotics</p> <p><i>Definition of infection:</i> Wound infection (proven with bacteriological confirmation, or suspected); remote infection</p> <p>Number of patients: 272</p>	<p><b>Cefradine</b> Dosage: 1 g at induction, then 8 and 16 h postoperation Route: i.v.</p> <p>Additional drugs: metronidazole, 1 g, rectally, also given</p> <p>Other details: second intraoperative dose given for operations lasting over 3 h</p> <p><b>Teicoplanin</b> Dosage: 6 mg/kg at induction Route: i.v.</p> <p>Other details: second intraoperative dose</p>	<p><b>Cefradine</b> Number evaluated: 136 % male: 64 Age (years): 65 ± 9</p> <p><i>Risk factors:</i> Diabetes n = 8 Recent vascular surgery n = 3</p> <p><b>Teicoplanin</b> Number evaluated: 136 % male: 69 Age (years): 63.7 ± 10.3</p> <p><i>Risk factors:</i> Diabetes n = 9 Recent vascular surgery n = 4</p>	<p><b>Cefradine</b> SSI: clinical signs of wound infection: 17/136; proven wound infection (30 days): 7/136; proven wound infection (2 months): 1/136</p> <p><i>MRSA/bacteria:</i> Gram-positive (30 days) (<i>S. aureus</i>): 2/136; polymicrobial (30 days): 2/136 [<i>S. aureus</i> + <i>P. mirabilis</i> (1); no details (1)] Gram-negative: 3/136 (30 days); 1/136 (2 months)</p> <p>Infection (other): respiratory tract: 9/136</p> <p>Mortality: all-cause 6/136 Caused by infection 1/136</p> <p>Duration of post-operative stay (days): 20.8</p>	<p>One patient was 12 years old. Incidence of infection by surgery type also reported. Not clear whether stay is post-operative or total. No AEs were considered definitely related to study drug. Surgery on the lower extremities had the highest risk of infection. Rates of infection were significantly higher for the general surgery ward, compared with a specialty vascular ward</p> <p><i>Quality assessment</i> 1. Unclear 2. Sealed envelopes 3. No 4. Yes</p>

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
	Follow-up: 1, 2, 7 and 28 days after surgery, with a long-term follow-up at least 6 months after surgery MRSA prevalence: not reported	given for operations lasting over 3 h	<i>Surgery details:</i> <b>Cephradine</b> Aneurysm, other site 6/136 Aortic aneurysm 2/136 Aortic aneurysm/femoro-popliteal graft 1/136 Aorto-femoral bypass 16/136 Axillo-femoral bypass 2/136 Carotid surgery 15/136 Femoro-popliteal graft 47/136 Graft, other site 5/136 Not vascular surgery 1/136 Profundaplasty 10/136 Y-graft 12/136 <b>Teicoplanin</b> Aneurysm, other site 2/136 Aortic aneurysm 26/136 Aortic aneurysm/femoro-popliteal graft 9/136 Aorto-femoral bypass 1/136 Axillo-femoral bypass 26/136 Carotid surgery 49/136 Femoro-popliteal graft 9/136 Graft, other site 0/136 Not vascular surgery 7/136 Profundaplasty 6/136 Y-graft	<b>Teicoplanin</b> SSI: clinical signs of wound infection: 15/136; proven wound infection (30 days): 5/136; proven wound infection (3 months): 1/136 <i>MRSA/bacteria:</i> Gram-positive (30 days) ( <i>S. aureus</i> ): 1/136; polymicrobial (30 days): 1/136 ( <i>S. aureus</i> + <i>Klebsiella aerogenes</i> ); Gram-positive (3 months) ( <i>S. aureus</i> ): 1/136 Gram-negative: 3/136 Infection (other): respiratory tract: 8/136 Mortality: all-cause 6/136 Caused by infection 2/136 Duration of post-operative stay (days): 15.4 Adverse events: <b>Cephradine</b> Patients with an event 39/136 Patients with event possibly or probably related to drug 15/136 Abnormal laboratory values 5/136 Allergic-type event 2/136 Cardiac events 7/136 Gastrointestinal disturbances 4/136 Haematoma, embolism or thrombosis 8/136 Non-cardiac vascular events 6/136	5. Yes 6. No 7. No 8. Yes 9. Yes 10. Yes Conclusion: a single dose of teicoplanin shows similar efficacy to three doses of cefradine plus metronidazole as prophylaxis for wound infection in vascular surgery

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
<p>Kirziz, 1991<sup>16</sup>                      France                      Setting: unclear                      Speciality: vascular</p>	<p><i>Inclusion criteria:</i>                      Undergoing vascular surgery involving the groin                      Number of patients: 202                      MRSA prevalence: not reported</p>	<p><b>Cefamandole</b>                      Dosage: 3 doses; exact dose not reported                      Route: not reported  <b>Vancomycin</b>                      Dosage: 2 g/day over 3 days                      Route: not reported                      Other details: serum immunological assays were performed to achieve trough levels &gt; 10–15 µg/ml</p>	<p><b>Cefamandole</b>                      Number evaluated: 104  <b>Vancomycin</b>                      Number evaluated: 98</p>	<p><b>Teicoplanin</b>                      Patients with an event 40/136                      Patients with event possibly or probably related to drug 19/136                      Abnormal laboratory values 7/136                      Allergic-type events 3/136                      Cardiac events 9/136                      Gastrointestinal disturbances 2/136                      Haematoma, embolism or thrombosis 10/136                      Non-cardiac vascular events 3/136</p>	<p>Conference abstract, many details not reported. It appears that patients were undergoing repeat (redux) surgery  <i>Quality assessment</i>                      Not enough information to assess quality  <i>Conclusion</i>                      Study shows the efficacy of vancomycin for prophylaxis</p>

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
Maki, 1992 <sup>21</sup> USA Setting: teaching hospital Specialty: cardiac vascular	<b>Inclusion criteria:</b> Adults undergoing cardiac or major vascular operations. <b>Exclusion criteria:</b> Renal disease; evidence of infection at time of surgery; known adverse reaction to $\beta$ -lactams or vancomycin <b>Definition of infection:</b> Postoperative surgical wound infection [purulent discharge from the wound; cellulitis associated with systemic signs of infection; sternal osteomyelitis, mediastinitis, prosthetic valve endocarditis (cardiac), prosthetic graft infection (vascular)]; mediastinitis (positive culture of mediastinal fluid); sternal osteomyelitis (persistent purulent drainage from sternotomy wound with microbiological confirmation); other (bacteraemia, tracheobronchitis or pneumonia, urinary tract, fungal and colitis) Number of patients: 334 Follow-up: daily during hospitalisation and at least 3 months after discharge Surgical site preparation: showered with 4% chlorhexidine; operative sites shaved and disinfected with 10% povidone-iodine	<b>Cefamandole</b> Dosage: 2 g starting 30 minutes before incision, then every 6 h for 48 h Route: i.v. Other details: controlled infusion over 60 minutes <b>Cefazolin</b> Dosage: 1 g starting 30 minutes before incision, then every 6 h for 48 h Route: i.v. Other details: controlled infusion over 60 minutes <b>Vancomycin</b> Dosage: 15 mg/kg or 1 g (whichever was greater) starting 30 minutes before incision, then 500 mg every 6 h for 48 h Route: i.v. Other details: controlled infusion over 60 minutes	<b>Cefamandole</b> Number evaluated: 113 % male: 83 Age (years): 59 Risk factors: Diabetes <i>n</i> = 19 <b>Cefazolin</b> Number evaluated: 114 % male: 82 Age (years): 60 Risk factors: Diabetes Vancomycin Number evaluated: 107 % male: 79 Age (years): 60 Risk factors: Diabetes <i>n</i> = 15 Other infections: Gram-positive (total): 9/113; <i>S. aureus</i> 1/113; MRSE 1/113; CNS 3/113; enterococci 2/113 Gram-negative: 3/113 <i>n</i> = 15 Diabetes Surgery details: <b>Cefamandole</b> Aortic aneurysm CABG Other cardiac operations Other vascular operations Prosthetic valve replacement Vascular bypass graft Duration of vascular surgery (minutes) 225 $\pm$ 92 Duration of cardiac surgery (minutes) 306 $\pm$ 93 <b>Cefazolin</b> Aortic aneurysm CABG 15/114 72/114	<b>Cefamandole</b> SSI (during hospitalisation): Cardiac: surgical wound infection: 6/83 (chest: 3; leg: 3); prosthetic valve endocarditis: 1/83 Vascular: surgical wound infection 7/30; prosthetic graft infection: 1/30 MRSA/bacteria SSI: Gram-positive (total): 7/113; <i>S. aureus</i> 1/113; MRSE (prosthetic graft: infection): 1/113; CNS 3/113; enterococci 2/113 Gram-negative: 3/113 Other infections: Gram-positive (total): 9/113; <i>S. aureus</i> 1/113; MR-CNS 2/113; CNS 3/113, enterococci 5/113 Gram-negative: 7/113 Infection (other): bacteraemia 1/113; oropharyngeal candidiasis (7 days) 2/113; tracheobronchitis/pneumonia 6/113; urinary tract 6/113 Duration of post-operative stay (days): 11 $\pm$ 6.5 <b>Cefazolin</b> SSI (during hospitalisation): Cardiac: surgical wound infection: 9/87 (chest: 6; leg: 3) Vascular: surgical wound infection: 5/27	Staphylococci with a minimal inhibitory concentration >4 $\mu$ g/ml were considered methicillin resistant, although no MRSA infections were identified. None of the Gram-positive organisms from any of the three groups was resistant to vancomycin. With respect to MRSA colonisation of the skin, the vancomycin and cefamandole patients had significantly lower levels of MR-CNS 5 days after surgery but at discharge the numbers were similar with over 75% of patients showing heavy colonisation. Blood concentrations of the drugs were measured in a subgroup of patients <b>Quality assessment</b> 1. Unclear 2. Not reported 3. Unclear 4. Yes 5. Yes 6. Unclear 7. Yes 8. Yes 9. Unclear 10. Yes <b>Conclusion</b> The administration of vancomycin immediately preoperatively provides therapeutic blood levels for surgical prophylaxis throughout most cardiac and vascular

continued



Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
	<p>Pre-operative screening: hematocrit; white blood, differential and platelet counts; SMA12 biochemistry profile; urinalysis. 10 cm<sup>2</sup> of skin in chest anterior area cultured within 4 h of admission to measure colonisation by MR and MS staphylococci</p> <p>MRSA prevalence: not reported</p>		<p>Other cardiac operations 6/114</p> <p>Other vascular operations 6/114</p> <p>Prosthetic valve replacement 15/114</p> <p>Vascular bypass graft 10/114</p> <p>Duration of vascular surgery (minutes) 219 ± 85</p> <p>Duration of cardiac surgery (minutes) 295 ± 100</p> <p><b>Vancomycin</b></p> <p>Aortic aneurysm CABG 7/107</p> <p>67/107</p> <p>Other cardiac operations 5/107</p> <p>Other vascular operations 6/107</p> <p>Prosthetic valve replacement 11/107</p> <p>Vascular bypass graft 17/107</p> <p>Duration of vascular surgery (minutes) 234 ± 94</p> <p>Duration of cardiac surgery (minutes) 319 ± 135</p>	<p><b>MRSA/bacteria</b></p> <p>SSI: Gram-positive (total): 9/114; MR-CNS 1/114; CNS 7/114; enterococci 2/114</p> <p>Gram-negative: 2/114</p> <p>Other infections: Gram-positive (total): 3/114; CNS 1/114; enterococci 2/114</p> <p>Gram-negative: 15/114</p> <p>Infection (other): bacteraemia 2/114; oropharyngeal candidiasis (7 days) 1/114; tracheobronchitis/pneumonia 4/114; urinary tract 1/114</p> <p>Duration of post-operative stay (days): 12.9 ± 8.6</p> <p><b>Vancomycin</b></p> <p>SSI (during hospitalisation) Cardiac: surgical wound infection (leg): 2/78</p> <p>Vascular: surgical wound infection: 2/29</p> <p><b>MRSA/bacteria</b></p> <p>SSI: Gram-positive (CNS): 2/107</p> <p>Other infections: Gram-positive (total): 4/107; <i>S. aureus</i> 1/107; CNS 3/107</p> <p>Gram-negative: 15/107</p> <p>Infection (other): bacteraemia 2/107; oropharyngeal candidiasis (7 days) 1/107; tracheobronchitis/pneumonia 9/107; urinary tract 6/107</p> <p>Duration of post-operative stay (days): 10.1 ± 6.1</p>	<p>operations, resulting in protection against postoperative infection that is superior to cefazolin or cefamandole</p>

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
				Adverse events: <b>Cefamandole</b> Hypotension during preoperative administration 3/113 Patient removed from study due to hypotension 2/113 Serum creatinine: Preoperative 1.14 ± 0.26 Postoperative day 7 1.12 ± 0.29	
				<b>Cefazolin</b> <i>C. difficile</i> antibiotic-associated colitis 2/114 Hypotension during preoperative administration 2/114 Maculopapular rash 3/114 Serum creatinine: Preoperative 1.16 ± 0.23 Postoperative day 7 1.15 ± 0.25	
				<b>Vancomycin</b> Hypotension during postoperative administration 2/107 Hypotension during preoperative administration 6/107 Maculopapular rash 1/107 Patient removed from study due to hypotension 3/107 Serum creatinine: Preoperative 1.1 ± 0.22 Postoperative day 7 1.15 ± 0.25	

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
Marroni, 1999 <sup>22</sup> Italy Setting: teaching hospital Specialty: vascular	<b>Inclusion criteria:</b> Adults scheduled for abdominal aortic and lower-extremity peripheral vascular surgery <b>Exclusion criteria:</b> Received antimicrobial agents in 5 days prior to surgery; preoperative areas of wet gangrene, cellulitis or open ulcer; allergy to glycopeptides or cephalosporins <b>Definition of infection:</b> CDC definitions: prosthetic and wound infections (primary endpoint); other postoperative infections (bloodstream, urinary tract, pneumonia) Number of patients: 238 Follow-up: daily during hospitalisation, every 3 months for a minimum of 1 year MRSA prevalence: 5/298 (1.7%) prosthetic vascular infections in 1994 of which 3 were methicillin-resistant (CNS or <i>S. aureus</i> )	<b>Cefazolin</b> Dosage: 2 g at induction Route: i.v. Other details: no dose adjustments made for body weight or renal failure <b>Teicoplanin</b> Dosage: 400 mg at induction Route: i.v. Other details: no dose adjustments made for body weight or renal failure	<b>Cefazolin</b> Number evaluated: 119 % male: 92 Age (years): 70 ± 8 Risk factors: ASA 3 Chronic obstructive pulmonary disease Diabetes Emergency surgery Normal renal function Revision surgery n = 104 n = 18 n = 6 n = 9 n = 98 n = 8 <b>Teicoplanin</b> Number evaluated: 119 % male: 93 Age (years): 68 ± 9 Risk factors: ASA 3 Chronic obstructive pulmonary disease Diabetes Emergency surgery Normal renal function Revision surgery n = 100 n = 12 n = 16 n = 0 n = 90 n = 8	<b>Cefazolin</b> SSI: superficial wound infection (30 days): 2/119 MRSA/bacteria SSI: polymicrobial (MSSA + <i>P. mirabilis</i> ): 1/119 Infection (other): bloodstream (central venous catheter-related): 3/119; pneumonia: 8/119; urinary tract (catheter-related): 3/119 Mortality: all-cause: 3/119; from infection (bloodstream): 1/119 <b>Teicoplanin</b> SSI: superficial wound infection (30 days): 5/119; graft infection (within 3 months of surgery): 2/119 MRSA/bacteria SSI: polymicrobial (CNS + <i>P. mirabilis</i> ): 1/119 Gram-negative: 1/119 Graft infection: Gram-positive (MSSA): 1/119 Infection (other): bloodstream (central venous catheter-related): 0/119; pneumonia: 8/119; urinary tract (catheter-related): 4/119 Mortality: all-cause: 4/119; from infection (prosthetic-related): 1/119 Duration of surgery (minutes): 188	No AEs relating to the infusion of the drugs were reported. Costs were reported. <b>Quality assessment</b> 1. Yes 2. Random permuted blocks 3. Unclear 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Unclear 10. Yes <b>Conclusion</b> The two treatments were similar in terms of efficacy

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments	
Mollan, 1992 <sup>26</sup> UK Setting: unclear Specialty: orthopaedic	<i>Inclusion criteria:</i> Over 14 years old and undergoing primary total hip or knee arthroplasty <i>Exclusion criteria:</i> Known glycopeptide or cephalosporin hypersensitivity, pregnancy or lactation, hepatic or renal impairment, pyrexia, urinary infection, antibiotic therapy in the past 7 days, emergency surgery, immunosuppression <i>Definition of infection:</i> Microbiologically documented wound infection was defined as a primary failure and divided into major and minor categories. Minor: superficial infection (e.g. suture line inflammation). Major: evidence of wound sepsis, deep abscess, osteomyelitis or other frank local infection. Secondary failure involved signs of infection remote from the wound Number of patients: 850	<b>Cephmandole</b> Dosage: 2 g at induction, 1 g at 6, 12 and 18 h Route: i.v. <b>Teicoplanin</b> Dosage: 400 mg at induction Route: not reported	<b>Teicoplanin</b> Abdominal aortic reconstruction 70/119 Aortofemoral bypass 21/119 graft Extra-anatomical 5/119 Infrainguinal surgery 23/119 Duration of surgery 214 (minutes)	<b>Cephmandole</b> Number evaluated: 352 <b>Teicoplanin</b> Number evaluated: 308 <i>Surgery details:</i> <b>Cephmandole</b> THR 270/352 TKR 82/352 <b>Teicoplanin</b> THR 242/308 TKR 66/308	<b>Cephmandole</b> SSI: any SSI (8–10 days): 2/352; major infection: 2/352 Infection (other): remote infection (8–10 days): 38/352 MRSA/bacteria (8–10 days): Gram-positive: 2/352 <b>Teicoplanin</b> SSI: any SSI (8–10 days): 2/308; major infection: 1/308; minor infection: 1/308 Infection (other): remote infection (8–10 days): 30/308 MRSA/bacteria (8–10 days): Gram-positive: 2/308 <i>Adverse events:</i> <b>Cephmandole</b> Pruritis/flushing 1/407 Vomiting 1/407 <b>Teicoplanin</b> Nausea, vomiting and erythema 1/394	850 patients enrolled; efficacy data for 660 reported. Interim analysis, no final report published <i>Quality assessment</i> 1. Unclear 2. Not reported 3. Unclear 4. Unclear 5. Yes 6. Yes 7. Unclear 8. Unclear 9. Unclear 10. No <i>Conclusion</i> Single-dose teicoplanin is a safe and effective prophylactic agent in prosthetic joint implant surgery

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
<p>Periti, 1999<sup>24</sup> Italy Setting: multi-centre Specialty: orthopaedic</p>	<p>Follow-up: 30 days and 6–18 months MRSA prevalence: not reported <i>Surgical procedures:</i> All patients received gentamicin-containing bone cement. Standard total hip replacement procedures by the posterior approach or a standard knee replacement with midline incision and medial approach were performed in all patients</p>	<p><b>Cefazolin</b> Dosage: 2 g at induction, then 1 g at 6, 12, 18 and 24 h Route: i.v. <b>Teicoplanin</b> Dosage: 400 mg at induction Route: i.v.</p>	<p><b>Cefazolin</b> Number evaluated: 424 % male: 31 Age (years): 64.7 ± 11.2 <i>Risk factors:</i> Diabetes mellitus n = 27 Performance status n = 47 fair/poor Previous LRTI n = 40 Previous UTI n = 46 <b>Teicoplanin</b> Number evaluated: 422 % male: 31 Age (years): 66 ± 9.7 <i>Risk factors:</i> Diabetes mellitus n = 27 Performance status n = 40 fair/poor Previous LRTI n = 39 Previous UTI n = 43</p>	<p><b>Cefazolin</b> SSI: any SSI (during hospitalisation): 7/424; any SSI (3 months): 3/364; any SSI (12 months): 1/343 MRSA/bacteria During hospitalisation: Gram-positive (<i>S. aureus</i>): 4/424 Gram-negative: 2/424 Infection (other): Bacteriuria: 9/424; fever &gt; 38°C: 41/424; lower respiratory tract: 1/424; thrombophlebitis: 2/424; urinary tract: 2/424 Duration of post-operative stay (days): 23 ± 12 <b>Teicoplanin</b> SSI: any SSI (during hospitalisation): 6/422; any SSI</p>	<p><i>Quality assessment</i> 1. Unclear 2. Not reported 3. Unclear 4. Yes 5. Yes 6. Yes 7. Unclear 8. Yes 9. Unclear 10. Yes <i>Conclusion</i> A single preoperative dose of teicoplanin gives results comparable to a standard multiple-dose regimen of cefazolin</p>

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
Pons, 1993 <sup>28</sup> USA Setting: teaching hospital Specialty: neurosurgery	Latent deep infection: pain restricting joint movement, increased erythrocyte sedimentation rate Number of patients: 860 Follow-up: daily during hospitalisation and 3 and 12 months after surgery Pre-operative screening: blood indices, protein levels and biochemical parameters; urine specimens sent for culture before operation MRSA prevalence: not reported		Surgery details: <b>Cefazolin</b> THR 348/424 TKR 76/424 Duration of surgery (THR) (minutes) 95.6 ± 37.4 Duration of surgery (TKR) (minutes) 116 ± 46.8 Operating theatre (conventional) 330/424 Operating theatre (hypersterile) 90/424 <b>Teicoplanin</b> THR 347/422 TKR 75/422 Duration of surgery (THR) (minutes) 93.9 ± 34 Duration of surgery (TKR) (minutes) 117.7 ± 40.7 Operating theatre (conventional) 331/422 Operating theatre (hypersterile) 84/422	(3 months): 3/375; any SSI (12 months): 1/340 MRSA/bacteria During hospitalisation: Gram-positive (total): 3/422; <i>S. aureus</i> : 1/422; CNS: 1/422 Gram-negative: 1/422 Infection (other): Bacteriuria: 3/422; fever >38°C: 36/422; lower respiratory tract: 4/422; thrombophlebitis: 2/422; urinary tract: 4/422 Duration of post-operative stay (days): 24.4 ± 13.7 Adverse events: <b>Cefazolin</b> Patients with a drug-related AE Erythema 1/424 Rash 1/424 <b>Teicoplanin</b> No AEs reported	Bacteria causing secondary pneumonias were reported: 7/19 pneumonias and 7/25 UTIs caused by Gram-negative bacteria; 5 pneumonias and 7 UTIs caused by Gram-positive bacteria (including <i>S. aureus</i> ); and all 5 i.v.-related infections caused by <i>S. aureus</i> . Primary wound infection rates were higher after spinal surgery, and
			<b>Ceftizoxime</b> Number evaluated: 422 Risk factors: Diabetes n = 18 <b>Vancomycin</b> Number evaluated: 404 Risk factors: Diabetes n = 15	<b>Ceftizoxime</b> SSI: primary wound infection (30 days): 5/422 MRSA/bacteria Gram-positive (total): 4/422; <i>S. aureus</i> : 1/422 Infection (other): i.v. related: 2/422; pneumonia: 7/422; urinary tract: 15/422	
		<b>Ceftizoxime</b> Dosage: 2 g, 1 h before incision Route: i.v. <b>Vancomycin</b> Dosage: 1 g given over 45 minutes, 1 h before incision Route: i.v. Additional drugs: plus 80 mg of gentamicin			
	<b>Inclusion criteria:</b> 18 years or older undergoing a cranial, spinal or transphenoidal neurosurgical procedure <b>Exclusion criteria:</b> Received antibiotics in the previous 24 h; pregnant or lactating women; undergoing permanent shunt or foreign body implant; known allergy to				

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
	study drugs or penicillin; existing infection or contaminated incision site; cirrhosis or severe renal or hepatic failure <i>Definition of infection:</i> Primary: superficial and deep incisional infection; stitch abscess; cellulitis (diagnosed by spreading induration and erythema at incision site); meningitis, brain abscess, empyema or osteomyelitis (all diagnosed by positive culture). Secondary: pneumonia (purulent sputum and infiltrate); urinary tract or infections relating to i.v. line (both diagnosed by positive culture)		<i>Surgery details:</i> <b>Ceftizoxime</b> Cranial 215/422 Re-operation 69/422 Spinal 142/422 Transsphenoidal 65/422 Use of operating microscope 391/422 Use of temporary CSF drain 33/422  <b>Vancomycin</b> Cranial 191/404 Re-operation 91/404 Spinal 149/404 Transsphenoidal 64/404 Use of operating microscope 376/404 Use of temporary CSF drain 27/404	<b>Vancomycin</b> SSI: primary wound infection (30 days): 5/404 <i>MRSA/bacteria</i> Gram-positive ( <i>S. aureus</i> ): 2/404 Infection (other): i.v. related: 3/404; pneumonia: 12/404; urinary tract: 10/404 <i>Adverse events:</i> <b>Ceftizoxime</b> Patients with an ADR 0/422 (red man syndrome) Blood urea nitrogen (mg/dl): Preoperative 13.51 ± 4.78 Postoperative 11.92 ± 4.79 Serum creatinine (mg/dl): Preoperative 0.91 ± 0.22 Postoperative 0.83 ± 0.21  <b>Vancomycin</b> Patients with an ADR 6/404 (red man syndrome) Blood urea nitrogen (mg/dl): Preoperative 14.96 ± 4.22 Postoperative 14.42 ± 5.24 Red man syndrome 6/404 Serum creatinine (mg/dl): Preoperative 0.86 ± 0.2 Postoperative 0.8 ± 0.18	also after new surgery through a previous incision. Baseline patient data and duration of hospitalisation were not reported. Antibiotic concentrations in blood and cerebrospinal fluid were reported for 19 patients <i>Quality assessment</i> 1. Yes 2. Computer program (Lotus 1-2-3) 3. Unclear 4. Unclear 5. Yes 6. Yes 7. Unclear 8. No 9. Unclear 10. Yes <i>Conclusion</i> Ceftizoxime is as effective as vancomycin and gentamicin in neurosurgical prophylaxis, but less toxic and penetrates CSF better
	Number of patients: 910 <i>Follow-up:</i> daily during hospitalisation, then for 3 months after discharge by monthly telephone interviews <i>Pre-operative screening:</i> Urinalysis and blood tests performed in first 186 patients only, before and 48 h after surgery MRSA prevalence: not reported <i>Surgical procedures:</i> Surgical procedures were never varied for study-related reasons				

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
Ratto, 1990 <sup>29</sup> Italy Setting: teaching hospital Specialty: thoracic	<b>Inclusion criteria:</b> Undergoing elective pulmonary resection for lung cancer <b>Exclusion criteria:</b> Allergy to antibiotics; preoperative evidence of a suppurative process in the chest; active infection at a site distant from the surgical site; antibiotic treatment within a week of thoracotomy; alcoholism, cirrhosis, malnutrition or severe renal dysfunction <b>Definition of infection:</b> Wound infection: a wound which appeared inflamed, containing exudate or purulent material. Pleural space: bacteria cultured from pleural fluid or tip of chest drain (contaminated); corpuscular, purulent material drained from space (infected). Lower respiratory tract: presence of roentgenographic and clinical signs of a new pulmonary infiltrate. The effectiveness of prophylaxis was assessed as the rate of either contamination or infection of the pleural space Number of patients: 102 Follow-up: inspected twice daily during postoperative hospitalisation	<b>Teicoplanin (long-term)</b> Dosage: as for short-term group then continued every 12 h until removal of pleural drains Route: i.v. Additional drugs: plus 1 g aztreonam <b>Teicoplanin (short-term)</b> Dosage: 6 mg/kg at induction, then another 2 doses of 3 mg/kg every 8 h Route: i.v. Additional drugs: plus 1 g aztreonam	<b>Teicoplanin (long-term)</b> Number evaluated: 25 % male: 84 Age (years): 59 ± 8.3 <b>Teicoplanin (short-term)</b> Number evaluated: 24 % male: 79 Age (years): 56 ± 9.1 <b>Surgery details:</b> <b>Teicoplanin (long-term)</b> Lobectomy 20/25 Pneumonectomy 4/25 Wedge 1/25 <b>Teicoplanin (short-term)</b> Lobectomy 17/24 Pneumonectomy 5/24 Wedge 2/24	<b>Teicoplanin (long-term)</b> SSI (during hospitalisation): wound infection: 1/25; empyema: 1/25; positive pleural fluid culture: 2/25 <i>MRSA/bacteria</i> Wound and pleural space infections: Gram-positive ( <i>S. aureus</i> ): 2/25; polymicrobial ( <i>S. epidermidis</i> + <i>Enterobacter</i> ): 2/25 Infection (other): lower respiratory tract: 3/25 Mortality 1/25 <b>Teicoplanin (short-term)</b> SSI (during hospitalisation): wound infection: 0/24; empyema: 2/24; positive pleural fluid culture: 7/24 <i>MRSA/bacteria</i> Wound and pleural space infections: Gram-positive (total): 9/24; <i>S. aureus</i> : 7/24 Infection (other): lower respiratory tract: 5/24 Adverse events: <b>Teicoplanin (long-term)</b> Postoperative diarrhoea 3/25 <b>Teicoplanin (short-term)</b> Postoperative diarrhoea 1/24	Patients were randomised to short- or long-term prophylaxis and within these groups blindly received antibiotics or placebo ( <i>n</i> = 53). The mean duration of surgery was approximately 180 minutes for each group. Mean length of stay for patients with infectious complications was 13 days and for those without complications 8 days. All isolated organisms were sensitive to teicoplanin <b>Quality assessment</b> 1. Unclear 2. Not reported 3. Unclear 4. Yes 5. Yes 6. Yes 7. Yes 8. Unclear 9. Unclear 10. Yes <b>Conclusion</b> Antibiotic prophylaxis is effective in reducing wound infections and short-term prophylaxis is the best regimen. Prolonged prophylaxis showed no advantage in preventing wound infections except in patients with pleural drainage lasting more than 4 days

continued



Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
Saginur, 2000 <sup>18</sup> Canada Setting: multi-centre Specialty: cardiac	<p>Pre-operative screening: cultures for aerobic and anaerobic bacteria taken from the bronchus (at surgical division), pleural space (before chest closure), pleural fluid (at drain removal)</p> <p>MRSA prevalence: not reported</p> <p><i>Surgical procedures:</i> A standardised sterile surgical technique was used. Skin towels and a clean technique for bronchial resection were used. Gloves were changed after bronchial suture and the pleural space was washed with warm saline at the end of surgery</p> <p><i>Inclusion criteria:</i> 18 years or over, having elective CABG, valve replacement or repair, or both</p> <p><i>Exclusion criteria:</i> Pregnancy; previous sternotomy; immunocompromised; morbidly obese; patients with osteotomies; medically unstable; allergy to study drugs; systemic AB in previous week; active bacterial infection; creatinine &gt;2.8 mg/dl or neutropenia &lt;1000 cells/mm<sup>3</sup></p>	<p><b>Cefazolin</b> Dosage: 2 g preoperatively, then 1 g every 8 h for 6 doses Route: i.v.</p> <p><b>Teicoplanin</b> Dosage: 15 mg/kg within 30 minutes of skin incision, then placebo every 8 h for 6 doses Route: i.v.</p>	<p><b>Cefazolin</b> Number evaluated: 1509 % male: 80 Age (years): 61.4 ± 10.2 <i>Risk factors:</i> Diabetes n = 300</p> <p><b>Teicoplanin</b> Number evaluated: 1518 % male: 80 Age (years): 61.6 ± 10.2 <i>Risk factors:</i> Diabetes n = 287</p> <p><i>Surgery details:</i> <b>Cefazolin</b> CABG 1227/1509 CABG and valve repair/replacement 84/1509</p>	<p><b>Cefazolin</b> SSI (30 days): any SSI: 155/1509; superficial sternal wound: 44/1509; superficial donor site: 84/1509; deep donor site: 9/1509; deep thoracic: 18/1509</p> <p>SSI (cumulative at 6 months): any SSI 179/1509; superficial sternal wound: 50/1509; superficial donor site: 97/1509; deep donor site: 13/1509; deep thoracic: 19/1509</p> <p>MRSA/bacteria: SSI: Gram-positive (total): 60/1509; CNS: 20/1509; CPS: 26/1509; enterococci/other: 14/1509</p>	<p>Study was interrupted at one centre when an outbreak of MRSA occurred. 5/82 strains of <i>S. aureus</i> and 42/84 strains of <i>S. epidermidis</i> were resistant to methicillin (not reported by treatment group). None of the Gram-positive strains causing wound infections were resistant to teicoplanin, whereas 8.3% were resistant to cefazolin</p> <p><i>Quality assessment</i> 1. Yes 2. Stratified randomisation performed by independent statistician 3. Yes 4. Yes</p>

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
	<p><i>Definition of infection:</i> Superficial thoracic (cellulitis and/or discharge); deep thoracic (deep wound infection needing debridement/drainage, sternal osteomyelitis, mediastinitis, endocarditis or pericarditis); donor site (superficial or deep); bacteraemia; respiratory tract infection; UTI</p> <p>Number of patients: 3047</p> <p>Follow-up: discharge, 1 month and 6 months</p> <p>Pre-operative screening: blood counts, serum creatinine, urine cultures</p> <p>MRSA prevalence: low</p>		<p>Valve repair/replacement 198/1509</p> <p>Chlorexidime skin preparation 549/1509</p> <p>Providone skin preparation 848/1509</p> <p>Duration of operation (hours) 3.9 ± 1.1</p> <p>Blood loss (ml) 752.9 ± 483.3</p> <p><b>Teicoplanin</b></p> <p>CABG 1240/1518</p> <p>CABG and valve repair/replacement 89/1518</p> <p>Valve repair/replacement 189/1518</p> <p>Chlorexidime skin preparation 567/1518</p> <p>Providone skin preparation 850/1518</p> <p>Duration of operation (hours) 3.9 ± 1</p> <p>Blood loss (ml) 786.9 ± 592.9</p>	<p>Gram-negative: 27/1509</p> <p><i>Infection (other):</i> 30 days: Bacteraemia: 11/1509; respiratory tract: 71/1509; urinary tract: 27/1509</p> <p>6 months: bacteraemia: 11/1509; respiratory tract: 81/1509; urinary tract: 34/1509</p> <p>Mortality: all-cause: 35/1520; with ongoing infection: 12/1520</p> <p>Morbidity: MI: 34/1520; pulmonary embolism: 6/1520; stroke: 20/1520</p> <p>Duration of post-operative stay (days): 9.5 ± 6.7</p> <p>Re-hospitalisation 297/1509</p> <p>Re-operation 42/1509</p> <p><b>Teicoplanin</b></p> <p>SSI (30 days): any SSI: 174/1518; superficial sternal wound: 71/1518; superficial donor site: 68/1518; deep donor site: 4/1518; deep thoracic: 31/1518;</p> <p>SSI (cumulative at 6 months): any SSI: 206/1518; superficial sternal wound: 80/1518; superficial donor site: 86/1518; deep donor site: 4/1518; deep thoracic: 36/1518;</p> <p><i>MRSA/bacteria:</i> SSI: Gram-positive (total): 83/1518; CNS: 56/1518; CPS: 22/1518; enterococci/other: 5/1518</p>	<p>5. Yes</p> <p>6. Yes</p> <p>7. Yes</p> <p>8. Unclear</p> <p>9. Yes</p> <p>10. Yes</p> <p><i>Conclusion</i> Cefazolin was more effective than teicoplanin as prophylaxis against postoperative wound infections. The infection rates were low with either treatment</p>

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
				Gram-negative: 21/1518 <i>Infection (other):</i> 30 days: bacteraemia: 15/1518; respiratory tract 116/1518; urinary tract: 114/1518 6 months: bacteraemia: 18/1518; respiratory tract: 127/1518; urinary tract: 122/1518 Mortality: all-cause: 35/1527; with ongoing infection: 14/1527 Morbidity: MI: 40/1527; pulmonary embolism: 8/1527; stroke: 19/1527 Duration of post-operative stay (days): 10 ± 7.9 Re-hospitalisation 320/1518 Re-operation 52/1518 Adverse events: <b>Cefazolin</b> Anaphylactic shock 1/1509 Hypotension 5/1509 Nausea 22/1509 Rash 3/1509 Vomiting 11/1509 <b>Teicoplanin</b> Anaphylactic shock 1/1518 Hypotension 3/1518 Nausea 30/1518 Rash 4/1518 Vomiting 12/1518	

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
Salminen, 1999 <sup>19</sup> Finland Setting: teaching hospital Specialty: cardiac	<b>Inclusion criteria:</b> Patients undergoing elective heart surgery <b>Exclusion criteria:</b> Serum creatinine > 17 mg/l <b>Definition of infection:</b> Wound infection: purulent discharge. Mediastinitis: clinical signs and results of cultures (wound and blood) and computed tomography Bacteriuria: bacterial growth > 100,000 cfu/ml. Respiratory: fever and pulmonary infiltration on chest X-rays Number of patients: 200 Follow-up: during hospitalisation, then via a questionnaire 2 months after discharge Pre-operative screening: chest X-ray; C-reactive protein; creatinine and haemoglobin levels; white blood cell count; alkaline phosphatase; liver transaminase; urinalysis with bacterial culture MRSA prevalence: not reported <b>Surgical procedures:</b> Most patients (189) underwent CABG; 2 had composite graft repair; 7 had aortic valve replacement; 1 had mitral valve repair; and 1 had reconstruction of the ascending aorta	<b>Ceftriaxone</b> Dosage: 2 g 45–60 minutes before incision Route: i.v. <b>Vancomycin</b> Dosage: 500 mg 45–60 minutes before incision, then every 6 h for 48 h Route: i.v.	<b>Ceftriaxone</b> Number evaluated: 97 % male: 72 Age (years): 70.1 ± 7.6 <b>Risk factors:</b> Asthma n = 2 Chronic bronchitis n = 1 Diabetes n = 23 Preoperative bacteriuria n = 8 <b>Vancomycin</b> Number evaluated: 103 % male: 71 Age (years): 68.9 ± 9.2 <b>Risk factors:</b> Asthma n = 4 Chronic bronchitis n = 4 Diabetes n = 14 Pre-operative bacteriuria n = 2 <b>Surgery details:</b> <b>Ceftriaxone</b> Cardiopulmonary 77.3 ± 27 bypass time (minutes) 54.9 ± 21.4 Ischaemic time (minutes) 56.5 ± 26.6 <b>Vancomycin</b> Cardiopulmonary 80.3 ± 33.4 bypass time (minutes) 56.5 ± 26.6 Ischaemic time (minutes) 56.5 ± 26.6	<b>Ceftriaxone</b> SSI (during hospitalisation): donor site infection: 1/97; mediastinitis: 1/97; sternal wound infection: 2/97 <i>MRSA/bacteria</i> Sternal wound: Gram-positive (total): 1/97; MRSA: 0/97; CNS: 1/97. Anaerobes: 1/97 Mediastinitis: Gram-positive (CNS): 1/97 Infection (other): respiratory (7 days): 2/97; urinary tract: 7/97 <b>Vancomycin</b> SSI (during hospitalisation): donor site infection: 1/103; sternal wound infection: 4/103 <i>MRSA/bacteria</i> Sternal wound: Gram-positive (total): 3/103; MRSA: 0/103; CNS: 3/103 Gram-negative : 1/103 Infection (other): respiratory (7 days): 2/103; urinary tract: 4/103	No MRSA infections and no significant AEs were reported. No severe infections occurred after discharge. 35 patients (no further details reported) received postoperative antibiotics. Overall hospital mortality was 4% (8 patients) <b>Quality assessment</b> 1. No 2. Alternation using date of birth 3. No 4. Yes 5. Yes 6. Unclear 7. Unclear 8. Yes 9. Unclear 10. Yes <b>Conclusion</b> A single 2-g dose of systemic ceftriaxone appears to provide good prophylaxis against wound infections, and the infection rates between the 2 groups were similar

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
Suter, 1994 <sup>25</sup> Italy Setting: general hospital Specialty: orthopaedic	<b>Inclusion criteria:</b> 18 years or older undergoing elective THR <b>Exclusion criteria:</b> Allergy to cephalosporins or glycopeptides, pregnancy or lactation, renal insufficiency, local or systemic infection, treatment with antibiotics in previous 2 weeks <b>Definition of infection:</b> Primary: deep infection or infection of prosthetic implant. Secondary: wound complications (infectious wound complications defined as purulent or culture-positive serous exudate, or superficial haematoma with positive cultures); respiratory tract infection; urinary tract infection; febrile morbidity	<b>Cefamandole</b> Dosage: 2 g 60–90 minutes before surgery, then 1 g at the end of surgery Route: i.v. <b>Teicoplanin</b> Dosage: 400 mg 60–90 minutes before surgery Route: i.v.	<b>Cefamandole</b> Number evaluated: 246 % male: 30 Age (years): 68.2 ± 8.1 <b>Risk factors:</b> Rheumatoid arthritis n = 4 Total (diabetes, venous insufficiency, renal failure, cirrhosis, cancer) n = 47 <b>Teicoplanin</b> Number evaluated: 250 % male: 26 Age (years): 66.5 ± 8.8 <b>Risk factors:</b> Rheumatoid arthritis n = 10 Total (diabetes, venous insufficiency, renal failure, cirrhosis, cancer) n = 45 <b>Surgery details:</b> <b>Cefamandole</b> Duration of surgery (minutes) 85 <b>Teicoplanin</b> Duration of surgery (minutes) 85	<b>Cefamandole</b> SSI (during hospitalisation): infectious wound complications: 4/246; non-infected haematoma: 4/246; serous non-infected exudate: 0/246; wound erythema: 3/246 MRSA/bacteria Gram-positive (total): 4/246; MSSA: 1/246 <b>Teicoplanin</b> Infection (other): febrile morbidity: 170/246; remote infection (virus): 1/246; respiratory tract: 7/246; urinary tract: 13/246 Morbidity: pulmonary embolism: 2/246 Mortality: all-cause: 2/260 Duration of post-operative stay (days): 17.11 ± 5.02	No deep infections involving the prosthesis occurred during hospitalisation and no late infections occurred <b>Quality assessment</b> 1. Yes 2. Random numbers table 3. Unclear 4. Yes 5. Yes 6. Unclear 7. Unclear 8. No 9. Unclear 10. Unclear <b>Conclusion</b> Single-dose teicoplanin is as effective as a multiple-dose regimen of cefamandole
	<b>Number of patients:</b> 520 <b>Follow-up:</b> during hospitalisation and for at least 12 months <b>Surgical site preparation:</b> shaving (disposable razor); cleaning with antiseptic soap; povidone-iodine solution applied for 5 minutes MRSA prevalence: not reported <b>Surgical procedures:</b> All procedures performed by the same two surgeons in conventional operating theatre	<b>Indication for surgery:</b> femoral neck fracture: 32/246; osteoarthritis: 209/246; osteonecrosis: 1/246; rheumatoid arthritis: 4/246 <b>Teicoplanin</b> Duration of surgery (minutes) 83 <b>Indication for surgery:</b> femoral neck fracture: 16/250; osteoarthritis: 222/250; osteonecrosis: 2/250; rheumatoid arthritis: 10/250	<b>SSI (during hospitalisation):</b> infectious wound complications: 0/250; non-infected haematoma: 8/250; serous non-infected exudate: 1/250; wound erythema: 4/250 <b>Infection (other):</b> febrile morbidity: 156/250; remote infection (virus): 1/250; respiratory tract: 7/250; urinary tract: 12/250 Morbidity: pulmonary embolism: 0/250 Mortality: all-cause: 0/260		

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
Vuorisalo, 1998 <sup>20</sup> Finland Setting: teaching hospital Specialty: cardiac	<i>Inclusion criteria:</i> Undergoing CABG without valve surgery <i>Exclusion criteria:</i> Known allergy to cephalosporins or vancomycin; active infection; prescribed antibiotics during previous 2 weeks; undergoing repeat bypass <i>Definition of infection:</i> CDC criteria: superficial incisional SSI (donor site or chest area); organ space SSI (mediastinitis) Number of patients: 1061 Follow-up: during hospitalisation and via a questionnaire 1 month after discharge Surgical site preparation: showered with 4% chlorhexidine scrub; mouth washed with chlorhexidine 0.2%; sites shaved and disinfected with alcoholic	<b>Cefuroxime</b> Dosage: 1.5 g at induction, then 0.75 g after 8 and 16 h Route: i.v. Other details: 1.5 g infused over 15 minutes <b>Vancomycin</b> Dosage: 1 g at induction, then 1 g after 12 h Route: i.v. Other details: slow infusion, 0.5 g/h over 2 h	<b>Cefuroxime</b> Number evaluated: 444 % male: 80 <i>Risk factors:</i> ASA 3 ASA 4-5 Asthma COPD Diabetes <b>Vancomycin</b> Number evaluated: 440 % male: 78 <i>Risk factors:</i> ASA 3 ASA 4-5 Asthma COPD Diabetes <i>Surgery details:</i> <b>Cefuroxime</b> Duration of operation (minutes) 248 <b>Vancomycin</b> Duration of operation (minutes) 249	<b>Cefuroxime</b> SSI (30 days): any SSI: 14/444; organ space (mediastinitis): 3/444; superficial chest: 7/444; superficial donor site: 4/444. Suspected (1 month after discharge): chest: 14/444; donor site: 61/444 <i>MRSA/bacteria:</i> Gram-positive (total): 14/444; MRSA: 0/444; CNS: 9/444; MR-CNS: 7/444; CPS: 2/444 Mortality: mediastinitis caused by MR-CNS: 1/444 Duration of post-operative stay (days): 11 <b>Vancomycin</b> SSI (30 days): any SSI: 15/440; organ space (mediastinitis): 2/440; superficial chest: 10/440; superficial donor site: 3/440. Suspected (1 month after discharge): chest: 12/440; donor site: 68/440	Duration of post-operative stay (days): 17.04 ± 6.55 <i>Adverse events:</i> <b>Cefamandole</b> Allergic reaction after first injection 2/260 <b>Teicoplanin</b> Allergic reaction to first injection 1/260 Median age in range 60-69 years. Numbers of suspected infections calculated from percentages given. AEs not reported in detail but no anaphylactic reactions or severe hypotension in either group. Study conducted 1992-3, organism prevalence rates reported for 1995-7 <i>Quality assessment</i> 1. Yes 2. Random number table 3. Unclear 4. Yes 5. Yes 6. Unclear 7. Unclear 8. No 9. Unclear 10. Yes <i>Conclusion</i> Vancomycin has no clinically significant advantages over cefuroxime in terms of infection prophylaxis

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
	<p>chlorhexidine 0.5%; sternotomy site covered with an iodine membrane</p> <p>MRSA prevalence: 1995–7: 0% (blood cultures); 0.2–0.4% (pus specimens); 0% (pus specimens from CABG patients)</p> <p><i>Surgical procedures:</i> Skin wounds closed with continuous non-resorbable monofilament sutures</p>			<p>MRSA/bacteria: Gram-positive (total): 11/440; MRSA: 0/440 CNS: 8/440; MR-CNS: 1/440; CPS: 2/440. Anaerobes: 2/440</p> <p>Mortality: MI: 2/440</p> <p>Duration of post-operative stay (days): 11</p>	
					<p>AB, antibiotics; COPD, chronic obstructive pulmonary disease; CSF, cerebrospinal fluid; LRTI, lower respiratory tract infection; MI, myocardial infarction; THR, total hip replacement; TKR, total knee replacement; UTI, urinary tract infection.</p> <p><sup>a</sup> Quality assessment items (all entries): 1. Was the assignment to treatment groups really random? 2. Method of randomisation. 3. Was the allocation of treatment concealed? 4. Were the groups similar at baseline? 5. Were eligibility criteria specified? 6. Were outcome assessors blinded to treatment? 7. Was the patient blinded to treatment? 8. Were analyses on an intention-to-treat basis? 9. Was there an appropriate sample size calculation? 10. Were withdrawals reported?</p>

## Studies included for adverse events only

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
Mercieri, 1999 <sup>30</sup> Italy Setting: teaching hospital Specialty: cardiac Study design: RCT	<b>Inclusion criteria:</b> Undergoing elective coronary artery surgery <b>Exclusion criteria:</b> Severe hypertension, diabetes, angiotensin-converting enzyme inhibitor therapy, surgical emergency, ejection fraction <40%, previous administration of aprotinin, allergy to study drugs, administration of radiological contrast medium in previous 72 h Number of patients: 100 <b>Surgical procedures:</b> Standard non-pulsatile hypothermic cardiopulmonary bypass (CBP)	<b>Cefamandole</b> Dosage: 2 g 30 minutes before surgery, then every 6 h for 48 h Route: i.v. Other details: diluted in 250 ml of saline <b>Cefamandole (plus aprotinin)</b> Dosage: 2 g 30 minutes before surgery, then every 6 h for 48 h Route: i.v. Additional drugs: plus high-dose aprotinin ( $2 \times 10^6$ kiu over 15 minutes at induction, then continuous infusion of $5 \times 10^5$ kiu/h plus an additional dose of $2 \times 10^6$ kiu added to CPB prime solution) <b>Vancomycin</b> Dosage: 15 mg/kg 3 h before surgery, 10 mg/kg after CPB interruption, then 15 mg/kg every 12 h for 48 h after surgery Route: i.v. Additional drugs: plus gentamicin 1.5 mg/kg after first vancomycin dose and every 8 h for 48 h after surgery	<b>Cefamandole</b> Number evaluated: 18 % male: 94 Age (years): 61 <b>Cefamandole (plus aprotinin)</b> Number evaluated: 22 % male: 91 Age (years): 61 <b>Vancomycin</b> Number evaluated: 21 % male: 90 Age (years): 62 <b>Vancomycin (plus aprotinin)</b> Number evaluated: 23 % male: 83 Age (years): 59 <b>Surgery details:</b> <b>Cefamandole</b> Duration of surgery (minutes) 250 ± 55 <b>Cefamandole (plus aprotinin)</b> Duration of surgery (minutes) 261 ± 53 <b>Vancomycin</b> Duration of surgery (minutes) 247 ± 56 <b>Vancomycin (plus aprotinin)</b> Duration of surgery (minutes) 265 ± 62	<b>Adverse events:</b> <b>Cefamandole</b> Acute renal failure (no dialysis required) Serum creatinine (mg/dl): Preoperative 1.01 ± 0.18 Postoperative 0.99 ± 0.31 day 7 Serum cystatin C (mg/l): Preoperative 1.06 ± 0.21 Postoperative 0.89 ± 0.22 day 7 <b>Cefamandole (plus aprotinin)</b> Acute renal failure (no dialysis required) Serum creatinine (mg/dl): Preoperative 0.95 ± 0.21 Postoperative 0.9 ± 0.16 day 7 Serum cystatin C (mg/l): Preoperative 1.02 ± 0.18 Postoperative 1.02 ± 0.2 day 7 <b>Vancomycin</b> Acute renal failure (no dialysis required) Serum creatinine (mg/dl): Preoperative 1.05 ± 0.18 Postoperative 1 ± 0.19 day 7 Serum cystatin C (mg/l): Preoperative 1.04 ± 0.25 Postoperative 0.93 ± 0.18 day 7	The effect of prophylaxis on kidney function was measured by serum creatinine level and cystatin C (a new, more sensitive marker). In the first week after surgery mean levels of both markers either remained constant or decreased slowly in all groups, except the vancomycin-gentamicin-protinin group, which experienced increases from day 2 onwards. This group had increased levels from day 2 onwards with a significant increase ( $p < 0.05$ compared with preoperative) in cystatin C at day 5 which peaked at day 7; a significant increase ( $p < 0.05$ ) in creatinine on days 6 and 7; and 39% of patients had a peak increase of both markers of at least 50% of basal values. There were no significant differences between groups with respect to urine output, serum electrolytes or blood urea nitrogen <b>Quality assessment</b> 1. Yes 2. Random numbers table 3. Unclear 4. Yes 5. Yes 6. Unclear 7. Unclear

continued



Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
Miro, 1996 <sup>15</sup> Spain Setting: teaching hospital Specialty: cardiac Study design: observational	Number of patients: 1394	Other details: diluted in 250 ml of saline and given over a minimum of 30 minutes <b>Vancomycin (plus aprotinin)</b> Dosage: vancomycin and gentamicin given as for the vancomycin-only group Additional drugs: plus aprotinin (as for the cefamandole plus aprotinin group)	<b>Teicoplanin</b> Number evaluated: 656 % male: not reported Age: not reported <b>Vancomycin</b> Number evaluated: 736 % male: not reported Age: not reported	<b>Vancomycin (plus aprotinin)</b> Acute renal failure 1/23 (no dialysis required) Serum creatinine (mg/dl): Preoperative 1.05 ± 0.16 Postoperative 1.28 ± 0.32 day 7 Serum cystatin C (mg/l): Preoperative 1.02 ± 0.11 Postoperative 1.45 ± 0.35 day 7	8. No 9. Unclear 10. Unclear
		<b>Teicoplanin</b> Dosage: 400 mg over 5 minutes preoperatively (valve replacement patients received 1 extra dose of 200 mg after surgery) Route: i.v. Additional drugs: plus 150 mg netilmicin (valve replacement patients received 2 extra doses of 150 mg every 12 h after surgery) <b>Vancomycin</b> Dosage: 1 g over 60 minutes preoperatively (valve replacement patients received 4 extra doses of 0.5 g every 6 h after surgery) Route: i.v. Additional drugs: plus 150 mg netilmicin (valve replacement patients received 2 extra doses of 150 mg every 12 h after surgery)		<b>Adverse events:</b> <b>Teicoplanin</b> Side-effects (severe hypotension, red man syndrome) <b>Vancomycin</b> Side effects (severe hypotension, red man syndrome)	Conference abstract of an open, non-randomised study (observational study with a historical control group). Patients in 1990–2 received vancomycin and patients in 1992–4 received teicoplanin. 832 patients had CABG and 562 valve replacement. Total number of patients receiving CABG or VR (1394) does not add up to sum of the two treatment groups (1392). Results were calculated from the reported percentages <i>Quality assessment</i> Not enough information to assess quality <i>Conclusion</i> Teicoplanin was as effective as vancomycin for preventing infections in patients undergoing cardiac surgery, but teicoplanin was better tolerated and easier to administer

continued

Study and setting	Study details	Interventions	Patient/procedure details	Results	Comments
Romanelli, 1993 <sup>31</sup> USA Setting: teaching hospital Specialty: cardiac Study design: RCT	<i>Inclusion criteria:</i> Adult patients requiring elective coronary bypass surgery <i>Exclusion criteria:</i> Valvular heart disease needing repair or replacement; history of prior open-heart surgery; LVEF <0.4; emergency surgery; chronic renal insufficiency (creatinine > 1.8 mg/dl) or failure; allergy to study drugs; chronic administration of calcium entry blockers; pregnancy Number of patients: 58	<b>Placebo</b> Dosage: 1 g before induction, then 1 g every 12 h until chest tubes discontinued (2 doses minimum) Route: i.v. Additional drugs: plus cefazolin (1 g preoperatively, 1 g in CPB machine solution, then 1 g every 6 h for a minimum of 48 h) Other details: slow infusion of normal saline <b>Vancomycin</b> Dosage: 1 g before induction, 500 mg in CPB machine solution, then 1 g every 12 h until chest tubes discontinued (2 doses minimum) Route: i.v. Additional drugs: plus cefazolin (1 g preoperatively, 1 g in CPB machine solution, then 1 g every 6 h for a minimum of 48 h) Other details: slow infusion (>30 minutes) in 250 ml of 5% dextrose solution	<b>Placebo</b> Number evaluated: 28 % male: 79 Age (years): 61 ± 11 <b>Vancomycin</b> Number evaluated: 30 % male: 73 Age (years): 59 ± 10 <i>Surgery details:</i> <b>Placebo</b> 28/28 CABG Duration of surgery (minutes) 334 ± 78 <b>Vancomycin</b> 30/30 CABG Duration of surgery (minutes) 307 ± 60	<i>Adverse events:</i> <b>Placebo</b> 4/28 Hypotension requiring a norepinephrine infusion <b>Vancomycin</b> 15/30 Hypotension requiring a norepinephrine infusion	There was no difference between groups in haemodynamic profiles obtained after the first dose of prophylaxis, or until initiation of cardiopulmonary bypass. Subsequent doses of vancomycin in the intra- and postoperative periods were associated with a significantly greater frequency of norepinephrine infusions to maintain normal haemodynamic indices. The vancomycin patients who required an infusion also had significantly lower mean systolic arterial pressure, mean arterial pressure and systemic vascular resistance compared with the placebo group <i>Quality assessment</i> 1. Unclear 2. Not reported. Schedule was prepared by the pharmacy 3. Unclear 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Unclear 10. Yes <i>Conclusion</i> Perioperative administration of vancomycin in cardiac surgery may result in hypotension requiring the use of a vasopressor in an attempt to normalise haemodynamic indices
CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction.					

## Appendix 5

### Data extraction tables: economic review

<b>Study, date of publication</b>	<b>Codina, 2000<sup>13</sup></b>
<b>Type of economic evaluation</b>	Cost-minimisation analysis
<b>Currency used, year</b>	Spanish pesetas, 1998
<b>Study design</b>	RCT, prospective single-centre double-blind parallel group
<b>Perspective</b>	Hospital
<b>Participants</b>	Age: teicoplanin group mean age 64 (years) (SD $\pm$ 11), vancomycin group 64 years (SD $\pm$ 12) Gender: teicoplanin group male/female 167/83, vancomycin group 167/83 Ethnicity: not stated Diagnosis: patients about to undergo elective cardiac surgery: either VR ( $n = 233$ ) or CABG ( $n = 267$ ) Exclusion criteria: allergy to glycopeptides or netilmicin; active infection; treatment with antibiotic in 5 days prior to surgery; renal insufficiency
<b>Screening for colonisation/ infection – diagnostic test details and results</b>	No
<b>Setting, country of study</b>	Hospital, Spain
<b>Type of surgery</b>	Clean
<b>Surgical site</b>	Cardiac
<b>Surgical environment</b>	Not stated
<b>Intervention group intervention</b>	Vancomycin ( $n = 250$ : CABG arm $n = 132$ , VR arm $n = 118$ )
<b>Method of administration of intervention (how administered, when, how long)</b>	Single i.v. 1-g dose at the induction of anaesthesia Patients undergoing VR received a second dose at the end of extracorporeal circulation
<b>Other interventions to reduce infection rates in the intervention group</b>	Also received netilmicin 150 mg and teicoplanin placebo
<b>Control I group intervention</b>	Teicoplanin ( $n = 250$ : CABG arm $n = 135$ , VR arm $n = 115$ )
<b>Method of administration of control I intervention</b>	Single i.v. 400 mg dose at the induction of anaesthesia Patients undergoing VR received a second dose (200 mg teicoplanin) at the end of extracorporeal circulation
<b>Other interventions to reduce infection rates in the control I group</b>	Also received netilmicin 150 mg and vancomycin placebo
<b>Resources used</b>	Drug use, the intravenous mix and the administration costs, personnel input, capital and overheads
<b>Source of effectiveness data</b>	Single study
<b>Length of follow-up</b>	Surgery period
<b>Source of resource use data</b>	Single study
<b>Source of unit cost data</b>	Hospital costs
<b>Link between cost and effectiveness data</b>	Prospective/concurrent
<b>Clinical outcomes measured and methods of valuation used</b>	All postoperative infections, based on CDC criteria

continued

<b>Exploration of antimicrobial resistance, including methods used</b>	No
<b>Outcome results/adverse drug events</b>	Total number of patients with an adverse drug event at first dose; vancomycin $n = 51/250$ , teicoplanin $n = 4/250$ Total number of patients with an AE (VR second dose; vancomycin $n = 6/118$ , teicoplanin $n = 1/115$ Severe hypotension; vancomycin $n = 1/250$ , teicoplanin $n = 1/250$
<b>Cost data handled appropriately</b>	Costs were reported separately from resource use. The source of the unit cost data was reported. Discounting was not relevant
<b>Cost results</b>	For the CABG patients, when the antibiotics were administered in the surgical room, the cost was 12,005 pts (1998 prices) for those who received vancomycin and 8265 pts for those who received teicoplanin. For the VP patients, when the antibiotics were administered in the surgical room, the cost was 14,528 pts for those who received vancomycin and 11,661 pts for those who received teicoplanin. When the antibiotics were administered in a medical ward setting, for the CABG patients, the cost was 2809 pts for those who received vancomycin and 6740 pts for those who received teicoplanin and for the VR patients, the cost was 10,140 pts for those who received vancomycin and 5308 pts for teicoplanin
<b>Subgroup analysis</b>	Two patient groups were considered, VR and CABG
<b>Modelling summary</b>	Decision tree analysis to calculate the costs associated with prophylaxis for the two patient groups
<b>Outcome measures used in the economic evaluation</b>	Severe AEs
<b>Direction of result with appropriate quadrant location</b>	Partial economic evaluation
<b>Statistical analysis for patient-level stochastic data</b>	Not undertaken
<b>Appropriateness of statistical analysis</b>	Not undertaken
<b>Uncertainty around cost-effectiveness expressed and appropriateness of method of dealing with uncertainty around this</b>	Not undertaken
<b>Sensitivity analysis and appropriateness</b>	Antibiotic administration in (1) the surgical theatre and (2) the medical ward. Due to the impact of staff costs and different resource use associated with administering either antibiotic, the use of teicoplanin was cheaper if administered in the surgical area whereas the use of vancomycin was cheaper if administered in the medical ward
<b>Modelling inputs and techniques appropriate</b>	Two simple decision trees were developed, one to evaluate the impact of the 2 interventions for VR patients, the other to evaluate the impact of the 2 interventions for CABG patients. Analyses were undertaken for medical room and surgery room administration of the drugs
<b>Authors' conclusions</b>	Outcomes were assumed to be the same across groups in terms of severe AEs. For the CABG patients, when the antibiotics were administered in the surgical room, the cost was 12,005 pts (1998 prices) for those who received vancomycin and 8265 pts for those who received teicoplanin. For the VR patients, when the antibiotics were administered in the surgical room, the cost was 14,528 pts for those who received vancomycin and 11,661 pts for those who received teicoplanin. When the antibiotics were administered in a medical ward setting, for the CABG patients, the cost was 2809 pts for those who received vancomycin and 6740 pts for those who received teicoplanin and for the VR patients, the cost was 10,140 pts for those who received vancomycin and 5308 pts for teicoplanin
<b>Implications for practice</b>	The costs of antibiotic prophylaxis among cardiac surgery patients depend heavily on the setting and the circumstances of drug administration. Teicoplanin was the least costly option when administered in the surgical theatre
<b>Comments</b>	No data on MRSA. Resistance issue not considered

*continued*

<b>Study, date of publication</b>	<b>Marroni, 1999<sup>22</sup></b>
<b>Type of economic evaluation</b>	Cost-minimisation analysis
<b>Currency used, year</b>	US\$, not stated
<b>Study design</b>	RCT, single-centre, double-blind
<b>Perspective</b>	Hospital
<b>Participants</b>	Age: teicoplanin group mean age 68 years (SD $\pm$ 9), cefazolin group 70 (SD $\pm$ 8) Gender: teicoplanin group male/female 111/8, cefazolin group 109/10 Ethnicity: not stated Diagnosis: patients about to undergo elective, clean abdominal or lower-limb prosthetic peripheral vascular surgery
<b>Screening for colonisation/infection – diagnostic test details and results</b>	No
<b>Setting, country of study</b>	Tertiary, Italy
<b>Type of surgery</b>	Clean
<b>Surgical site</b>	Cardiovascular
<b>Surgical environment</b>	Not stated
<b>Intervention group intervention</b>	Teicoplanin
<b>Method of administration of intervention</b>	Single 400-mg dose at the induction of anaesthesia
<b>Other interventions to reduce infection rates in the intervention group</b>	No
<b>Control 1 group intervention</b>	Cefazolin
<b>Method of administration of control 1 intervention (how administered, when, how long)</b>	Single 2-g dose at the induction of anaesthesia
<b>Other interventions to reduce infection rates in the control 1 group</b>	No
<b>Resources used</b>	Drug use and hospital stay
<b>Source of effectiveness data</b>	Single study
<b>Length of follow-up</b>	Until 1 year after hospital discharge, mean length 2 years
<b>Source of resource use data</b>	Single study
<b>Source of unit cost data</b>	Not stated
<b>Link between cost and effectiveness data</b>	Prospective/concurrent
<b>Clinical outcomes measured and methods of valuation used</b>	Rate of prosthetic and wound infections, overall mortality rate and side-effects
<b>Exploration of antimicrobial resistance, including methods used</b>	No
<b>Outcome results/adverse drug events</b>	5.9% ( $n = 7$ ) of the patients in the teicoplanin group developed SSI whereas 1.7% ( $n = 2$ ) patients in the cefazolin group developed infections. 1 patient had MSSA but was cured and had no sign of infection 2 years later. Early superficial wound infections, diagnosed a mean of 9 days post-operatively, occurred in 5 teicoplanin and 2 cefazolin patients. Other postoperative infections occurring postoperatively during the hospital stay included in 12 teicoplanin and 14 cefazolin patients. Mortality rates were similar, 4 (3.4%) in the teicoplanin group and 3 (2.5%) in the cefazolin group. Infective deaths amounted to 1 person in each group. No side-effects were observed in either group

continued

<b>Cost data handled appropriately</b>	The cost of drug acquisition and hospital stay was calculated. Costs were reported separately from resource use. The source of the unit cost data was not reported. Discounting was not relevant
<b>Cost results</b>	The total cost for the teicoplanin group was US\$52,510 higher than that for the cefazolin group
<b>Subgroup analysis</b>	No
<b>Modelling summary</b>	Not undertaken
<b>Outcome measures used in the economic evaluation</b>	Since the clinical effectiveness analysis demonstrated that there were no significant differences between the two interventions, the economic analysis was based on costs only
<b>Direction of result with appropriate quadrant location</b>	Partial evaluation. Authors stated that since there was no statistically significant difference in the effects, it was appropriate to compare costs only
<b>Statistical analysis for patient-level stochastic data</b>	Not undertaken
<b>Appropriateness of statistical analysis</b>	Not undertaken
<b>Uncertainty around cost-effectiveness expressed and appropriateness of method of dealing with uncertainty around this</b>	Not undertaken
<b>Sensitivity analysis and appropriateness</b>	Not undertaken
<b>Modelling inputs and techniques appropriate</b>	Not undertaken
<b>Authors' conclusions</b>	Teicoplanin is less toxic and requires less administration. No significant differences in infection rates but teicoplanin = 7 ( $n = 5.9\%$ ) patients develop infections, cefazolin = 2 ( $n = 1.7\%$ ). Mortality rates, teicoplanin = 4 (3.4%), refazolin = 3 (2.5%), no side-effects observed in either group. As no statistically significant differences in effects, did a cost-minimisation analysis. Cumulative total cost for teicoplanin = US\$571,572 vs cefazolin = US\$519,062. Drug and hospital stay costs were higher for teicoplanin. Cefazolin was more cost-effective. Cefazolin should remain the most appropriate choice for prophylaxis in patients undergoing vascular surgical procedures
<b>Implications for practice</b>	The transferability of the results was not discussed
<b>Comments</b>	No data on MRSA. Resistance issue not considered
<b>Study, date of publication</b>	<b>Phillips, 2000<sup>35</sup></b>
<b>Type of economic evaluation</b>	Cost-effectiveness analysis
<b>Currency used, year</b>	Canadian \$, price year not reported
<b>Study design</b>	Synthesis of published papers
<b>Perspective</b>	Hospital
<b>Participants</b>	Age: not stated Gender: not stated Ethnicity: not stated Diagnosis: hypothetical cohort of cardiovascular surgery patients who were labelled penicillin allergic
<b>Screening for colonisation/infection – diagnostic test details and results</b>	No
<b>Setting, country of study</b>	Tertiary, Canada
<b>Type of surgery</b>	Clean/clean contaminated/dirty
<b>Surgical site</b>	Cardiothoracic, vascular, gastrointestinal, orthopaedic, obstetric and gynaecological, head and neck, neurosurgery, urology, general surgery
<b>Surgical environment</b>	Clean air, standard, etc.

continued

<b>Intervention group intervention</b>	Vancomycin to all patients labelled penicillin allergic
<b>Method of administration of intervention (how administered, when, how long)</b>	Not stated
<b>Other interventions to reduce infection rates in the intervention group</b>	Not stated
<b>Control 1 group intervention</b>	Cefazolin to all patients labelled penicillin allergic
<b>Method of administration of control 1 intervention (how administered, when, how long)</b>	Not stated
<b>Other interventions to reduce infection rates in the control 1 group</b>	Not stated
<b>Control 2 group intervention</b>	Obtain a history from all patients labelled penicillin allergic and give vancomycin to all patients with a history suggesting an IgE-mediated reaction to penicillin, and cefazolin to all patients without a history of IgE-mediated reaction
<b>Method of administration of control 2 intervention (how administered, when, how long)</b>	Not stated
<b>Other interventions to reduce infection rates in the control 2 group</b>	Not stated
<b>Control 3 group intervention</b>	Administer penicillin skin test to patients with a history suggesting an IgE-mediated reaction to penicillin and give vancomycin to patients with a positive skin test and cefazolin to all others
<b>Method of administration of control 3 intervention (how administered, when, how long)</b>	Not stated
<b>Other interventions to reduce infection rates in the control 3 group</b>	Not stated
<b>Control 4 group intervention</b>	Administer a penicillin test to all patients labelled penicillin allergic and then give vancomycin to patients with a positive skin test and cefazolin to all patients with a negative skin test, regardless of history
<b>Method of administration of control 4 intervention (how administered, when, how long)</b>	Not stated
<b>Other interventions to reduce infection rates in the control 4 group</b>	Not stated
<b>Control 5 group intervention</b>	Administer a penicillin skin test to all patients labelled penicillin allergic then give vancomycin to patients with either a positive skin test or a history suggesting an IgE-mediated reaction to penicillin and give Cefazolin to all others
<b>Method of administration of control 5 intervention (how administered, when, how long)</b>	Not stated
<b>Other interventions to reduce infection rates in the control 5 group</b>	Not stated
<b>Resources used</b>	Drug use, cephalosporin skin test, treatment of serious reaction to drugs
<b>Type of study</b>	Decision analytic model
<b>Source of effectiveness data</b>	Based on previously published studies
<b>Source of adverse drug events</b>	Based on previously published studies
<b>Length of follow-up</b>	Not reported

continued

<b>Source of resource use data</b>	Not reported
<b>Source of unit cost data</b>	Based on actual data provided by Sunnybrook, a tertiary care centre
<b>Link between cost and effectiveness data</b>	Retrospective
<b>Clinical outcomes measured and methods of valuation used</b>	History suggesting an IgE-mediated reaction to penicillin (population labelled penicillin allergic), positive penicillin skin test (population labelled penicillin allergic with history suggesting IgE-mediated reaction to penicillin), serious non-life-threatening reaction to cefazolin (general population and population labelled penicillin allergic with negative penicillin test), serious non-life-threatening reaction to vancomycin, anaphylaxis to cefazolin (general population and population labelled penicillin allergic with negative penicillin skin test, anaphylaxis to vancomycin (general population)
<b>Exploration of antimicrobial resistance, including methods used</b>	No
<b>Outcome results/adverse drug events</b>	History suggesting an IgE-mediated reaction to penicillin (population labelled penicillin allergic) was 0.42 For positive penicillin skin test (population labelled penicillin allergic with history suggesting IgE-mediated reaction to penicillin 0.14 (range 0.10–0.18) Serious non-life-threatening reaction to cefazolin for general population 0.005 (range 0.005–0.029) for population labelled penicillin allergic with negative penicillin test 0.03 (range 0–0.03) Anaphylaxis to vancomycin (general population) 0.0002 (range 0–0.03)
<b>Cost data handled appropriately</b>	Unit cost details were reported but details on resource use were not provided. Discounting was not undertaken. The time frame of the study was not reported but is likely to have been too short to require discounting
<b>Cost results</b>	No costs were explicitly reported
<b>Subgroup analysis</b>	No
<b>Modelling summary</b>	Considering the rate of serious non-life-threatening reactions, strategy 2 dominated strategies 1 and 3. The incremental cost per reaction avoided with strategy 4 was Can\$5426. With strategy 5 the ICER was Can\$10,024. With strategy 6 the ICER was Can\$10,906 Considering anaphylaxis, the incremental cost per reaction avoided was Can\$166,667 with strategy 3, Can\$159,204 with strategy 1, Can\$428,571 with strategy 4, Can\$692,308 with strategy 5 and Can\$544,776 with strategy 6 when compared with strategy 2
<b>Outcome measures used in the economic evaluation</b>	Rate of serious non-life-threatening reactions and the rate of potentially life-threatening anaphylactic episodes
<b>Direction of result with appropriate quadrant location</b>	North-east
<b>Statistical analysis for patient-level stochastic data</b>	No
<b>Appropriateness of statistical analysis</b>	Not applicable
<b>Uncertainty around cost-effectiveness expressed and appropriateness of method of dealing with uncertainty around this</b>	Not applicable
<b>Sensitivity analysis and appropriateness</b>	All model variables were varied in the analysis. The ranges used were derived from the literature regarding probability values. No justification was provided for the variation in costs tested. The type of sensitivity analysis was not specified but is likely to be univariate
<b>Modelling inputs and techniques appropriate</b>	Yes

continued



<b>Authors' conclusions</b>	The decision analytic model indicated that selective use of vancomycin is more cost-effective than indiscriminate use of vancomycin for surgical prophylaxis in cardiovascular surgery patients labelled penicillin allergic
<b>Implications for practice</b>	The transferability of the results was not discussed
<b>Comments</b>	No data on MRSA. Resistance issue not considered
<b>Study, date of publication</b>	<b>Spelman, 2002<sup>36</sup></b>
<b>Type of economic evaluation</b>	Cost-effectiveness analysis
<b>Currency used, year</b>	Australian \$
<b>Study design</b>	Single-centred before-and-after study
<b>Perspective</b>	Hospital
<b>Participants</b>	Age: not stated Gender: not stated Ethnicity: not stated Diagnosis: patients undergoing CABG
<b>Screening for colonisation/infection – diagnostic test details and results</b>	No
<b>Setting, country of study</b>	Tertiary hospital, Australia
<b>Type of surgery</b>	Cardiac surgery for CABG
<b>Surgical site</b>	
<b>Surgical environment</b>	
<b>Intervention and its administration</b>	1g of vancomycin administered i.v. and 600 mg of oral rifampicin preoperatively. The oral rifampicin was administered in the ward prior to the operating room. The vancomycin was administered by the anaesthetist on the patient's arrival in the operating room. A second dose of vancomycin was administered 12 h postoperatively. Each vancomycin dose was infused during approximately 1 h
<b>Other interventions to reduce infection rates in the intervention group</b>	Not specified
<b>Control and its administration</b>	1g of cephazolin administered i.v. One dose preoperatively and 3 doses postoperatively
<b>Other interventions to reduce infection rates in control</b>	Not specified
<b>Resources used</b>	Not specified
<b>Source of effectiveness data</b>	Before-and-after study, single-centre
<b>Length of follow-up</b>	12 months before and 12 months after the change in antibiotic prophylaxis used in the hospital
<b>Source of resource use data</b>	Single study observational data
<b>Source of unit cost data</b>	Hospital
<b>Link between cost and effectiveness data</b>	Prospectively
<b>Clinical outcomes measured and methods of valuation used</b>	SSI rate after CABG according to causative organism (based on CDC definitions of SSI) MRSA MSSA Skin or enteric flora No growth or no specimen Enterobacteriaceae Other

continued

<b>Exploration of antimicrobial resistance, including methods used</b>	Not undertaken
<b>Outcome results/adverse drug events</b>	SSI rate from 10.5 (95% CI 8.2 to 13.3) with cephazolin to 4.9 (95% CI 3.2 to 7.1) with vancomycin and rifampicin infections per 100 procedures Surgical site infection rate after CABG according to causative organism MRSA cases: 42 = cephazolin, 0 = vancomycin and rifampicin MSSA: 5 = cephazolin, 2 = vancomycin and rifampicin Skin or enteric flora: 10 = cephazolin, 10 = vancomycin and rifampicin No growth or no specimen: 3 = cephazolin, 4 = vancomycin and rifampicin Enterobacteriaceae: 3 = cephazolin, 7 = vancomycin and rifampicin Other: 0 = cephazolin, 2 = vancomycin and rifampicin No adverse drug events were reported
<b>Cost data handled appropriately</b>	Unclear. The source of unit costs and resource use were not specified
<b>Cost results</b>	The vancomycin and oral rifampicin group were associated with a statistically significant decrease ( $p < 0.001$ ) in the SSI rate and this was estimated to result in a saving of Aus\$576,655 compared with the first 12 months of follow-up when the patients received cephazolin
<b>Subgroup analysis</b>	Not undertaken
<b>Modelling summary</b>	Not undertaken
<b>Outcome measures used in the economic evaluation</b>	The primary outcome measure in the economic evaluation was the deep sternal wound infection rate
<b>Direction of result with appropriate quadrant location</b>	Costs and benefits not synthesised but results suggest that vancomycin and rifampicin is the dominant strategy (south-east quadrant)
<b>Statistical analysis for patient-level stochastic data</b>	Infection rates were compared using a $\chi^2$ test. Statistical analysis of costs was not reported
<b>Appropriateness of statistical analysis</b>	Appropriate. No other tests were reported
<b>Uncertainty around cost-effectiveness expressed and appropriateness of method of dealing with uncertainty around this</b>	Not undertaken
<b>Sensitivity analysis and appropriateness</b>	Not undertaken
<b>Modelling inputs and techniques appropriate</b>	Not applicable
<b>Authors' conclusions</b>	Antibiotic prophylaxis using a combination of i.v. vancomycin and oral rifampicin for patients undergoing CABG surgery resulted in a statistically significant difference in the SSI rate ( $p < 0.001$ ) and costs saved of Aus\$576,655
<b>Implications for practice</b>	The transferability of the results was not discussed. Full details of all resources used and unit costs were not provided, which reduces the chance of applying the results to other settings
<b>Comments</b>	No data on MRSA. Resistance issue not considered
<b>Study, date of publication</b>	<b>Zanetti, 2001</b> <sup>37</sup>
<b>Type of economic evaluation</b>	Cost-effectiveness analysis, cost-utility analysis
<b>Currency used, year</b>	US\$, 1998
<b>Study design</b>	Controlled trials (unclear as to whether randomised) Base case: study population was a hypothetical cohort of 10,000 patients undergoing CABG surgery Synthesis of studies using a decision-analytic model

continued

	Reference case: 65-year-old man undergoing CABG surgery for stable multi-vessel coronary heart disease
	A state transition model was used to incorporate the lifetime probability of death, myocardial infarction, angina, or asymptomatic coronary heart disease following CABG surgery to estimate life expectancy, quality-adjusted life expectancy and total lifetime costs
<b>Perspective</b>	Base case: healthcare payer perspective
	Reference case: societal perspective
<b>Participants</b>	Age: Reference case 65 years old
	Gender: male
	Ethnicity: not studied
	Diagnosis: stable, multi-vessel coronary heart disease
<b>Screening for colonisation/ infection – diagnostic test details and results</b>	Not undertaken
<b>Setting, country of study</b>	Tertiary care, USA
<b>Type of surgery</b>	Clean/clean contaminated
<b>Surgical site</b>	Cardiothoracic
<b>Surgical environment</b>	Standard
<b>Intervention group 1</b>	Routine vancomycin as first line perioperative prophylaxis
<b>Method of administration</b>	5 doses of 1 g of vancomycin over 48 h
<b>Other interventions to reduce infection rates in the intervention group</b>	No
<b>Control group 1</b>	Routine cefazolin, reserving vancomycin for those with a history of allergic reaction to $\beta$ -lactam antibiotics
<b>Method of administration</b>	6 doses of 1 g of cefazolin over 48 h
<b>Other interventions to reduce infection rates in the intervention group</b>	No
<b>Control group 2</b>	No routine prophylaxis
<b>Method of administration</b>	Not applicable
<b>Other interventions to reduce infection rates in the intervention group</b>	No
<b>Resources used</b>	Intervention: vancomycin, staff time for preparation and administration of drug Control 1: cefazolin, staff time for administration of drug Control 2: not applicable
<b>Type of study</b>	
<b>Source of effectiveness data</b>	Multiple sources from the published literature, national databases and author assumption
<b>Source of adverse drug events</b>	Published literature
<b>Length of follow-up</b>	Base case: 3 months postoperatively Reference case: 5 years
<b>Source of resource use data</b>	4 published studies were used to provide resource use data associated with SSIs and hospital deaths. The resource use associated with AEs was based on a single study. The resource use associated with 5 years' follow-up were extrapolated from one published study
<b>Source of unit cost data</b>	4 published studies were used to provide cost data associated with SSIs and hospital deaths. The cost associated with AEs was based on a single study. The costs associated with 5 years' follow-up were extrapolated from one published study
<b>Link between cost and effectiveness data</b>	Retrospective

continued

<p><b>Clinical outcomes measured and methods of valuation used</b></p>	<p><b>Base case</b></p> <p>Number of hospital deaths avoided</p> <p>Number of deep SSIs avoided (based on CDC definitions)</p> <p>Number of superficial SSIs avoided</p> <p>Incidence of superficial SSI 0.08 (range 0.02–0.12)</p> <p>Incidence of deep SSI 0.04 (range 0.01–0.06)</p> <p>Causative organisms:</p> <p><i>S. aureus</i> 0.25 (range 0.20–0.35)</p> <p>CNS 0.25 (range 0.20–0.35)</p> <p>Enterococci 0.05 (range 0.02–0.15)</p> <p>Gram-negative bacteria 0.30 (range 0.15–0.50)</p> <p>RR of SSI caused by susceptible organisms:</p> <p>Vancomycin vs no prophylaxis 0.4 (range 0.20–0.80)</p> <p>Cefazolin vs no prophylaxis 0.4 (range 0.20–0.80)</p> <p>Incidence of SSI due to resistant organisms:</p> <p>MRSA (% of all SSI due to <i>S. aureus</i>) 0.012 (0.40) (range 0–0.03)</p> <p>MR-CNS (% of all SSI due to CNS) 0.024 (0.80) (range 0–0.03)</p> <p>VRE (% of all SSI due to enterococci) 0.003 (0.15) (range 0–0.006)</p> <p>Incidence of SSI caused by cefazolin-susceptible Gram-negative bacteria (% of all SSI due to Gram-negative bacteria) 0.01 (0.28) (range 0–0.036)</p> <p>History of <math>\beta</math>-lactams 0.1 (0.05 to 0.15)</p> <p>Probability of hospital death:</p> <p>Deep SSI 0.082 (range 0.01–0.10)</p> <p>Antibiotic allergic reaction 0.00002</p> <p>CABG surgery related events 0.036 (range 0.01–0.10)</p> <p><b>Reference case</b></p> <p>QALYs: quality weights were derived from the Beaver Dam Health Outcomes Study. Quality-adjusted life expectancy was estimated by applying quality weights to the health states representing death, myocardial infarction, angina, asymptomatic coronary artery disease. The quality weights were obtained from a published study which used time trade-off techniques to elicit utilities</p> <p>Future benefits were discounted at a rate of 3%</p>
<p><b>Exploration of antimicrobial resistance, including methods used</b></p>	<p>Impact of antimicrobial resistance explored in the sensitivity analysis not in the model</p> <p>The authors did conduct a simulation exercise to explore an increase in VRE by 2% per year; however, given the current lack of knowledge about glycopeptide resistance to staphylococci, they were unwilling to place any weight on this</p>
<p><b>Outcome results/adverse drug events</b></p>	<p><b>Base case</b></p> <p>Routine vancomycin deep SSI 368 and 388 hospital deaths per 10,000 patients. Compared with no prophylaxis, routine vancomycin resulted in 29 fewer deep SSI and 58 fewer superficial SSI and 3 fewer deaths</p> <p>Routine cefazolin deep SSI 397 and 391 hospital deaths per 10,000 patients. Compared with no prophylaxis, routine cefazolin resulted in 173 fewer deep SSI and 347 fewer superficial SSI and 14 fewer deaths</p> <p>No prophylaxis deep SSI 570 and 405 hospital deaths per 10,000 patients</p> <p><b>Reference case</b></p> <p>Routine vancomycin 8.339 QALYs or 0.004 incremental QALYs compared with cefazolin</p> <p>Routine cefazolin 8.335 QALYs or 0.023 incremental QALYs compared with no prophylaxis</p> <p>No prophylaxis 8.312 QALYs</p>

continued

<b>Adverse drug events</b>	<p>Incidence of antibiotic-related AEs</p> <p>Vancomycin 0.08 (range 0.01–0.20) (adjusted estimate reflecting the probability of toxicity with a 2-day prophylactic regimen by assuming a linear relationship between incidence of AEs and duration of therapy)</p> <p>Cefazolin 0.08 (range 0.01–0.20)</p>
<b>Cost data handled appropriately</b>	<p>Cost data were not reported separately from resource use data. No productivity losses were calculated for the reference case analysis even though the perspective was stated as societal</p> <p>Future costs were discounted at a rate of 3%</p>
<b>Cost results</b>	<p><b>Base case</b></p> <p>Routine vancomycin total cost per 10,000 patients was US\$23,360,000</p> <p>This resulted in an incremental saving of US\$1,170,000 per 10,000 patients from using cefazolin instead of no antibiotic prophylaxis</p> <p>Routine cefazolin total cost per 10,000 patients was US\$24,530,000</p> <p>No prophylaxis total cost per 10,000 patients was US\$33,410,000</p> <p>This resulted in an incremental saving of US\$8,880,000 per 10,000 patients from using cefazolin instead of no antibiotic prophylaxis</p> <p><b>Reference case</b></p> <p>Routine vancomycin total lifetime cost = US\$61,913</p> <p>Incremental saving of US\$103 if vancomycin used instead of cefazolin</p> <p>Routine cefazolin total lifetime cost = US\$62,016</p> <p>Incremental saving of US\$876 if cefazolin used instead of no prophylaxis</p>
<b>Subgroup analysis</b>	No
<b>Modelling summary</b>	Benefits and costs were not combined as the cefazolin strategy dominated the no prophylaxis strategy and the vancomycin strategy was as effective and cost-saving compared with cefazolin
<b>Direction of result with appropriate quadrant location</b>	Costs and benefits not synthesised as the cefazolin strategy dominated the no prophylaxis strategy. The vancomycin strategy was as cost-saving and as effective as the cefazolin strategy, but results suggest that vancomycin and rifampicin is the dominant strategy (south-east quadrant)
<b>Statistical analysis for patient-level stochastic data</b>	No
<b>Appropriateness of statistical analysis</b>	Costs were treated deterministically
<b>Uncertainty around cost-effectiveness expressed and appropriateness of method of dealing with uncertainty around this</b>	Not undertaken
<b>Sensitivity analysis and appropriateness</b>	<p><b>Base case</b></p> <p>Univariate and multivariate sensitivity analyses were undertaken to determine the impact of variability in the model input parameters. The plausible ranges (above) were used as parameters for testing for deaths from all causes and SSI-related deaths, distribution of causative organisms, incidence of prophylaxis-related AEs, proportion of patients with allergy to <math>\beta</math>-lactam antibiotics, costs of cefazolin, deep or superficial SSI, death or prophylaxis-related events. Results were most sensitive to changes in the cost of vancomycin, efficacy of cefazolin and vancomycin in preventing SSI, and prevalence of bacterial resistance to antibiotics</p> <p>A multi-way sensitivity analysis of the impact of different antibiotic susceptibility profiles was undertaken. Routine vancomycin remained the most effective and least costly strategy, independent of the prevalence of VRE</p>

continued

	<p><b>Reference case</b></p> <p>Results were most sensitive to the acquisition and administration cost of vancomycin, the efficacy of vancomycin and cefazolin in preventing SSIs and the prevalence of bacterial resistance to antibiotics</p> <p>Incidence of SSI due to resistant organisms:</p> <p>MRSA (% of all SSI due to <i>S. aureus</i>) 0.012 (0.40) (range 0–0.03)</p> <p>MR-CNS (% of all SSI due to CNS) 0.024 (0.80) (range 0–0.03)</p> <p>VRE (% of all SSI due to enterococci) 0.003 (0.15) (range 0–0.006)</p> <p>Incidence of SSI caused by cefazolin-susceptible Gram-negative bacteria (% of all SSI due to Gram-negative bacteria) 0.01 (0.28) (range 0–0.036)</p> <p>In the sensitivity analysis, the study explored the impact of different antibiotic susceptibility profiles on the results. A three-way sensitivity analysis of the impact of different antibiotic susceptibility profiles, that is, for MRSA, MR-CNS and cefazolin-susceptible Gram-negative bacteria, was undertaken. Routine vancomycin remained the most effective and least costly strategy, independent of the prevalence of VRE</p> <p>The impact of different patterns of antimicrobial resistance on the ICER associated with vancomycin compared with routine cefazolin was calculated</p> <p>For the base case analysis a decision analytic model was used and for the reference case a state transition model was used</p> <p>A strategy of no prophylaxis was always less effective and more costly than using prophylaxis. Use of routine vancomycin prior to CABG is more effective and cost-effective than cefazolin prophylaxis and no routine antibiotic prophylaxis prior to surgery</p> <p>Vancomycin rather than cefazolin should be used for routine prophylaxis prior to clean surgical procedures that would save lives and hospital costs. However, since the issue of resistance was not explored, the authors were reluctant to recommend a change in practice</p> <p>Resistance issue not considered</p>
<b>Modelling inputs and techniques appropriate</b>	
<b>Authors' conclusions</b>	
<b>Implications for practice</b>	
<b>Comments</b>	

## **Appendix 6**

### **Economic evaluation quality assessment**

	Codina, 2000 <sup>13</sup>	Marroni, 1999 <sup>22</sup>	Phillips, 2000 <sup>35</sup>	Spelman, 2002 <sup>36</sup>	Zanetti, 2001 <sup>37</sup>
<b>Cost effectiveness</b>					
<i>Study question</i>					
Were costs and effects examined?	✓	✓	✓	✓	✓
Alternatives compared	✓	✓	✓	✓	✓
Viewpoint/s clearly stated	✓	×	✓	✓	✓
<i>Selection of alternatives</i>					
All relevant alternatives compared?	✓	✓	✓	✓	✓
For the alternatives compared, were all clearly described?	✓	✓	✓	✓	✓
Rationale for choosing the alternative programmes compared is stated	✓	✓	✓	✓	✓
<i>Form of evaluation</i>					
Choice of form of economic evaluation is justified in relation to questions addressed	✓	✓	✓	✓	✓
If a cost-minimisation analysis is chosen, have equivalent outcomes been adequately demonstrated?	✓	✓	NU	NU	✓
<i>Effectiveness data</i>					
The source of effectiveness estimates used are stated	✓	✓	✓	✓	✓
Effectiveness data from RCT or review of RCTs	✓	✓	U	×	U
Potential biases identified	✓	✓	✓	✓	✓
Details of method of synthesis or meta-analysis of estimates are given	NA	NA	×	NA	✓
<i>Costs</i>					
All the important and relevant resource use included	✓	✓	✓	✓	✓
All the important and relevant resource use measured accurately	✓	✓	✓	✓	✓
Appropriate unit costs estimated	✓	U	✓	✓	✓
Unit costs reported separately from resource use data	✓	P	✓	×	×
If productivity costs were included, were they treated separately from other costs?	NA	NA	NA	NA	NA
The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion	✓	×	×	NA	NA
<i>Benefit measurement and valuation</i>					
The primary outcome measure for the economic evaluation is clearly stated	✓	✓	✓	✓	✓
Methods to value health states and other benefits are stated	NA	NA	NA	NA	✓
Details of the individuals from whom valuations were obtained are given	NA	NA	NA	NA	✓
<i>Decision modelling</i>					
Details of any model used are given	✓	NA	✓	NA	✓
The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	NA	✓	NA	✓
All model outputs described adequately	✓	NA	✓	NA	✓
<i>Discounting</i>					
Discount rate used for both costs and benefits	NA	NA	NA	NA	✓
Do discount rates accord with NHS guidance?	NA	NA	NA	NA	×

continued



	Codina, 2000 <sup>13</sup>	Marroni, 1999 <sup>22</sup>	Phillips, 2000 <sup>35</sup>	Spelman, 2002 <sup>36</sup>	Zanetti, 2001 <sup>37</sup>
<b>Allowance for uncertainty</b>					
<i>Stochastic analysis of patient-level data</i>					
Details of statistical tests and CIs are given for stochastic data	NA	NA	NA	NA	NA
Uncertainty around cost-effectiveness estimates expressed	NA	NA	NA	NA	NA
Sensitivity analysis used to assess uncertainty in non-stochastic variables and analytic methods	NA	NA	NA	NA	NA
<i>Stochastic analysis of decision models</i>					
Are all appropriate input parameters included with uncertainty?	NA	NA	NA	NA	✓
Is second-order uncertainty (uncertainty in means) included rather than first-order uncertainty (uncertainty between patients)?	NA	NA	NA	NA	×
Are the probability distributions adequately detailed and appropriate?	NA	NA	NA	NA	U
Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs) and analytic decisions (e.g. methods to handle missing data)	NA	NA	NA	NA	✓
<i>Deterministic analysis</i>					
The approach to sensitivity analysis is given	✓	NU	✓	NU	NA
The choice of variables for sensitivity analysis is justified	✓	NA	✓	NA	NA
The ranges over which the variables are varied are stated	✓	NA	✓	NA	NA
<i>Presentation of results</i>					
Incremental analysis is reported using appropriate decision rules	✓	✓	✓	✓	✓
Major outcomes are presented in both a disaggregated and an aggregated form	✓	✓	✓	✓	✓
Applicable to the UK setting	×	×	×	×	×
✓, yes; X, no; NA, not applicable; NU, not undertaken; P, partial; U, uncertain.					





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## Disease Prevention Panel

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### **Feedback**

The HTA Programme and the authors would like to know your views about this report.

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***We look forward to hearing from you.***