National Institute for Health and Care Excellence

Guideline version (Draft)

Surgical site infection: prevention and treatment

[C] Evidence reviews for application of intraoperative topical antiseptics and antibiotics before wound closure

NICE guideline CG74

Evidence reviews

[Month Year]

Draft for Consultation

These evidence reviews were developed by NICE Guideline Updates Team

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Effectiveness of intraoperative topical antiseptics and antibiotics before wound closure in the prevention of surgical site infection

Review question

Is the application of intraoperative topical antiseptics/antimicrobials before wound closure clinically effective in reducing surgical site infection rates?

It became apparent during the development of this update that the question above carried forward from the original guideline should specifically state antiseptics and antibiotics instead of the term 'antimicrobials'. This decision was based on committee input during the development of the review protocol. The committee noted that term 'antimicrobials' would encompass both antiseptics and antibiotics. The committee also agreed that term 'operative field' would be more appropriate as the application of the interventions included in this review can vary. Hence, the review question answered in this update (and to be carried forward in any future updates) was:

- Is the application of antiseptics and antibiotics in the operative field before wound closure clinically effective in reducing surgical site infection rates?

Introduction

Surgical site infections (SSIs) are serious postoperative complications. Antiseptics and antibiotics can be applied to the operative field before wound closure to reduce the risk of SSIs.

The 2008 NICE guideline on the prevention and treatment of surgical site infection recommended against the use of intraoperative skin re-disinfection or topical cefotaxime in abdominal surgery to reduce surgical site infection. This decision was driven by the evidence which demonstrated that the instillation of cefotaxime into wounds prior to closure appears to have no effect on SSI incidence after surgery for peritonitis.

The topic was reviewed in 2017 by NICE surveillance team and new evidence was identified which examined the use of topical antiseptics and antimicrobials before wound closure for the reduction in SSI, and thus prompted a partial update to review new evidence.

The review aims to evaluate the effective application of intraoperative antiseptics and antibiotics to the operative field before wound closure in the prevention of SSI.

This review identified studies that fulfilled the conditions specified in PICO table. For full details of the review protocol, see appendix A.

Table 1 PICO: Is the application of antiseptics and antibiotics in the operative field before wound closure clinically effective in reducing surgical site infection rates?

Population	People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery)
Interventions	• Different antibiotic classes used alone or included in bone cement during orthopaedic surgery (penicllins, cephalosporins,

	fluoroquinolones, aminoglycosides, monobactams, carbapanems, macrolides and vancomycin) • Gentamicin collagen sponges, beads and gel • Cefotaxime • Chlorhexidine • Iodine • Iodophors including povidone iodine.
Comparator	• No skin antiseptics/ antibiotics • Different antiseptics/ antibiotics • Placebo

Outcomes	• Surgical site infection (superficial, deep and organ/space SSI), including SSIs up to 30 days and 1 year, defined using appropriate criteria such as CDC SSI criteria.
	• Mortality post-surgery
	• Length of hospital stay
	• Postoperative antibiotic use.
	• Infectious complications such as septicaemia or septic shock
	• Adverse events:
	  ○ Antimicrobial resistance
	  ○ Kidney toxicity
	  ○ Anaphylaxis

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in appendix A and the methods section in appendix B.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

A search strategy was used to identify all studies that examined the effectiveness of intraoperative topical antiseptics and antibiotics (outlined in Table 1) applied to the operative field before wound closure to reduce the risk of SSIs. RCTs and systematic reviews of RCTs were considered for inclusion. The review protocol specified that in the event of less than 5 RCTs being identified, quasi randomised trials would also be considered for inclusion.

The search strategies used in this review are detailed in appendix C.

Studies were also excluded if they:

- Included patients undergoing a surgical procedure that does not involve a visible incision and therefore does not result in the presence of a conventional surgical wound
- Were not in English
- Were not full reports of the study (for example, published only as an abstract)

Data on overall SSI was extracted. Where possible, data on superficial, deep and organ/space SSI were also examined. According to the Centres for Disease Control and Prevention (CDC) a SSI is defined as an infection occurring within 30 days after operation. A deep SSI is defined as an infection which occurs within 30 days after the operation if no implant is left in place, or within 1 year if implant is placed. Therefore SSI within 30 days and 1 year were prioritised in this review.

Studies included in the review explored a number of different follow up periods. Two studies [Andersson 2010 and Collin 2013] reported outcomes at various time points. Therefore analysis was stratified by different follow up periods.

A number of different surgical procedures were explored in the studies included in the review. Where possible subgroup analysis was conducted based on surgical procedure. Furthermore, surgical procedures and wounds can be classified as the following:

- Clean –incision in which no inflammation is encountered in a surgical procedure, without a break in sterile technique, and during which the respiratory, alimentary and genitourinary tracts are not entered.
- Clean-contaminated – an incision through which the respiratory, alimentary or genitourinary tract is entered under controlled conditions but with no contamination encountered.
- Contaminated – an incision undertaken during an operation in which there is a major break in sterile technique or gross spillage from the gastrointestinal tract, or an incision in which acute, non-purulent inflammation is encountered. Open traumatic wounds that are more than 12–24 hours old also fall into this category
- Dirty or infected – an incision undertaken during an operation in which the viscera are perforated or when acute inflammation with pus is encountered during the operation (for example, emergency surgery for faecal peritonitis), and for traumatic wounds where treatment is delayed, and there is faecal contamination or devitalised tissue present.

Data on surgical wound classification was also extracted and subgroup analysis was conducted.

Clinical evidence

Included studies

From a database of 1,982 studies, 129 studies were identified from the literature search as being potentially relevant. Five additional studies were identified as being potentially relevant; 1 study from the 2008 NICE guideline on the prevention and treatment of surgical site infection, 1 study from the surveillance review and 3 additional studies from a systematic review [Konstantelias 2016]. Altogether, 134 studies were identified as being potentially relevant. Following full text review of the 134 studies, 30 RCTs were included.

For the search strategy, see appendix C. For clinical evidence study selection flowchart, see appendix D.

The included RCTS examined the following interventions:

- Gentamicin collagen sponges
- Povidone iodine spray
- Povidone iodine solution
- Vancomycin powder
- Cefotaxime
- Cephaloridine
- Antibiotic loaded bone cement (erythromycin and colistin loaded bone cement)
- Ampicillin powder
- Iodine solution (2.5% iodine in 70% ethanol)

Excluded studies

List of papers excluded at full text, with reasons for exclusion, is given in Appendix K.

1 Summary of clinical studies included in the evidence review.

2 The included studies are summarised in Table 2 below. See appendix E for full evidence
3 tables.

4 **Table 2 Summary of included studies**

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
Andersson (2010)	Local administration of antibiotics by gentamicin-collagen sponge does not improve wound healing or reduce recurrence rate after pilonidal excision with primary suture: a prospective randomized controlled trial	• Study location Sweden • Study setting Multicentre (performed across 11 hospitals) • Study dates March 2003 to November 2005 • Duration of follow-up Up to 3 months • Sources of funding Not reported	• Gentamicin collagen sponge	• No antibiotics No gentamicin collagen sponge was implanted.	• SSI
Bennett-Guerrero (2010a)	Gentamicin-collagen sponge for infection prophylaxis in colorectal surgery	• Study location US • Study setting Department of Surgery. • Study dates February 2008 and March 2009 • Duration of follow-up 60 days from surgery. • Sources of funding Supported by Innocoll Technologies.	• Gentamicin collagen sponge	• No antibiotics No gentamicin collagen sponge was placed in the control group.	• SSI • Superficial SSI • Deep SSI • Organ/space SSI • Length of hospital stay • Hospital readmission
Bennett-Guerrero (2010b)	Effect of an implantable gentamicin-collagen sponge on sternal wound infections following cardiac surgery: a randomized trial	• Study location US • Study setting Not specified. • Study dates 21st December 2007 to 11th March 2009 • Duration of follow-up 90 days from surgery. • Sources of funding Study was sponsored by Innocoll Technologies Ltd.	• Gentamicin collagen sponge	• No antibiotics The control group did not receive gentamicin collagen sponges.	• SSI • Superficial SSI • Deep SSI • Length of hospital stay • Hospital readmission

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
Buimer (2008)	Surgical treatment of hidradenitis suppurativa with gentamicin sulfate: a prospective randomized study	• Study location The Netherlands • Study setting Medical Centre • Study dates Not reported. • Duration of follow-up 1 week • Sources of funding Not specified.	• Gentamicin collagen sponge	• No antibiotics Hidradenitis suppurativa lesions were excised with primary closure of the wound without enclosure of antibiotics.	• SSI
Collin (2013)	Effect of local gentamicin-collagen on perineal wound complications and cancer recurrence after abdominoperineal resection: a multicentre randomized controlled trial.	• Study location Sweden • Study setting University hospital • Study dates February 2000 to April 2003 • Duration of follow-up 1, 3 and 12 months. • Sources of funding Not specified.	• Gentamicin collagen sponge	• No antibiotics Patients underwent surgery alone (no sponge implanted).	• SSI
Cordtz (1989)	The effect of incisional plastic drapes and redisinfection of operation site on wound infection following caesarean section	• Study location Denmark • Study setting Hospital setting • Study dates Not reported. • Duration of follow-up 2 weeks • Sources of funding Not reported	• 2.5% Iodine in 70% ethanol	• No antiseptics For pre-operative skin disinfection 2.5% iodine in 70% ethanol was used. The patients were randomised to receive no disinfection.	• SSI
Eklund (2005)	Prophylaxis of sternal wound infections with gentamicin-collagen implant: randomized controlled study in cardiac surgery	• Study location Finland • Study setting University hospital • Study dates July 1998 and September 1999 • Duration of follow-up 3 months • Sources of funding The study was supported by grants from Helsinki University Central Hospital and	• Gentamicin collagen sponge	• No antibiotics The controls' sternums were closed in a routine manner with steel wires, without gentamicin implants.	• SSI • Superficial SSI • Deep SSI • Organ/space SSI • Mortality post-surgery

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
		Schering Plough Corporation.			
Evans (1974)	The reduction of surgical wound infections by topical cephaloridine: a controlled clinical trial	• Study location UK • Study setting Hospital setting. • Study dates Not specified. • Duration of follow-up 4 weeks. • Sources of funding Glaxo Laboratories Ltd provided the cephaloridine (Ceporin).	• Cephaloridine	• No antibiotics No antibiotics were used before wound closure.	• SSI
Friberg (2005) Friberg (2007)	Local gentamicin reduces sternal wound infections after cardiac surgery: a randomized controlled trial	• Study location Sweden • Study setting Cardiothoracic centres • Study dates September 2000 to September 2002 • Duration of follow-up 2 months postoperatively • Sources of funding Study financed by grants from the Research Committee of Orebro County Council and from Schering-Plough, who also provided free Collamtamp-G.	• Gentamicin collagen sponge	• No antibiotics In the control group the wound was closed in a conventional way.	• SSI • Superficial SSI • Deep SSI • Mortality post-surgery
Gray (1981)	The effect of topical povidone iodine on wound infection following abdominal surgery	• Study location UK • Study setting Surgical Department • Study dates Not specified • Duration of follow-up 2 weeks • Sources of funding Not specified.	• Povidone Iodine	• No antiseptics	• SSI •Postoperative antibiotic use

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
Gruessner (2001)	Improvement of perineal wound healing by local administration of gentamicin-impregnated collagen fleeces after abdominoperineal excision of rectal cancer.	• Study location Germany • Study setting Not specified. • Study dates Not specified. • Duration of follow-up 8 weeks • Sources of funding Not specified.	• Gentamicin collagen sponge	• No antibiotics Control group received complete closure of the pelvic floor, mandatory insertion of a sacral overflow drain, and multiple-layer primary wound management.	• SSI
Haase (2005)	Subcutaneous gentamycin implant to reduce wound infections after loop-ileostomy closure: a randomized, double-blind, placebo-controlled trial	• Study location Germany • Study setting Department of General, visceral and thoracic surgery • Study dates May 2000 to June 2003 • Duration of follow-up within 30 days • Sources of funding Not specified.	• Gentamicin collagen sponge	• Placebo The collagen implant was placed subcutaneously	• SSI • Superficial SSI • Deep SSI
Harihara (2006)	Effects of applying povidone-iodine just before skin closure	• Study location Japan • Study setting Department of surgery. • Study dates July 2004 and December 2004 • Duration of follow-up Not specified. • Sources of funding No specified.	• Povidone Iodine .	• No antiseptics No antiseptic was used before skin closure.	• SSI
Hinarejos (2013)	The use of erythromycin and colistin-loaded cement in total knee arthroplasty does not reduce the incidence of infection: a prospective randomized study in 3000 knees	• Study location Spain • Study setting Departments of Orthopaedic Surgery and Infectious Diseases. • Study dates September 2005 to April 2010. • Duration of follow-up 12 months.	• Erythromycin and colistin-loaded cement	• No antibiotics Prosthesis was cemented with Simplex cement without antibiotic.	• SSI • Superficial SSI • Deep SSI

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
		• Sources of funding Not specified.			
Migaczewski (2012)	Prevention of early infective complications after laparoscopic splenectomy with the Garamycin sponge	• Study location Poland • Study setting not specified • Study dates September 2007 to December 2009 • Duration of follow-up 1 month (30 days) • Sources of funding not reported	• Gentamicin collagen sponge	• No antibiotics Following laparoscopic splenectomy, no sponge was left at the splenic site.	• SSI
Moesgaard (1989)	Intraincisional antibiotic in addition to systemic antibiotic treatment fails to reduce wound infection rates in contaminated abdominal surgery. A controlled clinical trial	• Study location Denmark • Study setting Department of surgical gastroenterology • Study dates April 1983 to January 1986 • Duration of follow-up One month • Sources of funding Not specified	• Cefotaxime	• No antibiotics No antibiotics were used before skin closure.	• SSI •Organ/space SSI • Infectious complication: septicaemia
Musella (2001)	Collagen tampons as aminoglycoside carriers to reduce postoperative infection rate in prosthetic repair of groin hernias.	• Study location Italy • Study setting University Hospital • Study dates January 1991 to January 1999 • Duration of follow-up 6 months • Sources of funding Not specified.	• Gentamicin collagen sponge	• No antibiotics Patients in the control group had a standard surgical treatment.	• SSI
Nowacki (2005)	Prospective, randomized trial examining the role of gentamycin-containing collagen sponge in the reduction of postoperative morbidity in rectal cancer patients:	• Study location Poland • Study setting not specified • Study dates January 1997 to April 1999 • Duration of follow-up 1 month (30 days) • Sources of	• Gentamicin collagen sponge	• No antibiotics No sponge was used.	• SSI

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
	early results and surprising outcome at 3-year follow-up	funding not reported			
Ozbalci (2014)	Is gentamicin-impregnated collagen sponge to be recommended in pilonidal sinus patient treated with marsupialization? A prospective randomized study	• Study location Turkey • Study setting Department of general Surgery • Study dates January 2011 and December 2012 • Duration of follow-up 6- 30 months • Sources of funding Not specified	• Gentamicin collagen sponge.	• No antibiotics Patients in this group did not receive gentamicin sponge.	• SSI
Parker (1985)	Systemic metronidazole combined with either topical povidone-iodine or ampicillin in acute appendicitis	• Study location UK • Study setting Hospital setting • Study dates Not specified. • Duration of follow-up 1 month • Sources of funding Napp laboratories supplied materials for study.	• Povidone Iodine	• Different antibiotics Ampicillin powder	• SSI
Pochhammer (2015)	Subcutaneous application of gentamicin collagen implants as prophylaxis of surgical site infections in laparoscopic colorectal surgery: a randomized, double-blinded, three-arm trial	• Study location Germany • Study setting Single centre • Study dates July 2008 to July 2010 • Duration of follow-up 1 month (30 days) • Sources of funding Authors reported that medical device manufacturers provided gentamicin-collagen and collagen-only sponges and no further funding was given.	• Gentamicin collagen sponge	• Placebo A collagen sponge without any antibiotics was inserted subcutaneously after closing the peritoneum and aponeurosis separately with a running polyglactin suture at the bowel extraction site • No antibiotics No sponge was placed at the surgical site.	• Superficial SSI • Deep SSI • Length of hospital stay
Rickett (1969)	Topical ampicillin in the	• Study location UK	• Vancomycin powder	• Placebo A phial	• SSI

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
	appendectomy wound: report of double-blind trial	• Study setting Not specified. • Study dates May and September 1968. • Duration of follow-up 3 weeks after surgery. • Sources of funding Beecham Research Laboratories supplied specially packaged phials of ampicillin and placebo.		(500mg) of placebo (lactose powder) was emptied into the muscle layers after closing peritoneum.	
Rutkowski (2014)	Surgical site infections following short-term radiotherapy and total mesorectal excision: results of a randomized study examining the role of gentamicin collagen implant in rectal cancer surgery	• Study location Poland • Study setting Department of Oncological gastroenterology • Study dates January 2008 to September 2011. • Duration of follow-up 90 days after operation. • Sources of funding Grant from the Ministry of Science and Higher Education Republic of Poland.	• Gentamicin collagen sponge	• No antibiotics In comparator group, no gentamicin collagen sponge was placed.	• SSI • Superficial and/or deep incisional SSI. •Organ/space SSI
Rutten (1997)	Prevention of wound infection in elective colorectal surgery by local application of a gentamicin-containing collagen sponge	• Study location The Netherlands • Study setting Department of Gastrointestinal surgery • Study dates May 1992 and May 1994 • Duration of follow-up Not specified. • Sources of funding Not specified.	• Gentamicin collagen sponge	• No antibiotics No gentamicin sponge	• SSI
Schimmer (2012)	Gentamicin-collagen sponge reduces sternal wound	• Study location Germany • Study setting Single centre	• Gentamicin collagen sponge	• Placebo After complete adaption of the pericardium	• SSI • Superficial SSI • Deep SSI

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
	complications after heart surgery: a controlled, prospectively randomized, double-blind study	• Study dates June 2009 to June 2010 • Duration of follow-up 1 month (30 days) • Sources of funding Authors stated that the study was supported by medical device manufacturers: RESORBAW Wundversorgung GmbH & Co KG		and preliminary placement of the sternal wiring, a placebo sponge, identical to the intervention sponge, was implanted retrosternally, without premoistening	
Sherlock (1984)	Combined preoperative antibiotic therapy and intraoperative topical povidone-iodine. Reduction of wound sepsis following emergency appendectomy	• Study location UK • Study setting Department of surgery. • Study dates Not reported • Duration of follow-up 4 weeks • Sources of funding Not specified.	• Povidone Iodine	• No antiseptics No antiseptic was added before skin closure.	• SSI
Tubaki (2013)	Effects of using intravenous antibiotic only versus local intrawound vancomycin antibiotic powder application in addition to intravenous antibiotics on postoperative infection in spine surgery in 907 patients	• Study location India. • Study setting Department of Orthopaedics and Spine Surgery. • Study dates June 2011 to December 2012. • Duration of follow-up 12 weeks. • Sources of funding Ganga Orthopaedic Research and Education Foundation.	• Vancomycin powder	• No antibiotics	• SSI • Superficial SSI • Deep SSI
Walsh (1981)	The effect of topical povidone-iodine on the incidence of infection in surgical wounds.	• Study location Australia • Study setting Department of surgery and clinical microbiology. • Study dates Not specified.	• Povidone Iodine	• No antiseptics	• SSI

Short Title	Title	Study details	Interventions	Comparator	Outcome measure(s)
		• Duration of follow-up 1 month. • Sources of funding F.H Faulding and Company for financial support and supplies of povidone iodine (Betadine).			
Westberg (2015)	Effectiveness of gentamicin-containing collagen sponges for prevention of surgical site infection after hip arthroplasty: a multicenter randomized trial	• Study location Norway • Study setting Multicentre (performed across 4 district general hospitals and 1 university hospital) • Study dates February 2011 to July 2013 • Duration of follow-up 1 month (4 weeks) • Sources of funding not reported	• Gentamicin collagen sponge.	• No antibiotics Following hemiarthroplasty, no collagen sponges were placed as investigators believed that they could theoretically act as a medium for bacterial growth.	• Superficial SSI • Deep SSI • Mortality post-surgery • Length of hospital stay
Yetim (2010)	Effect of local gentamicin application on healing and wound infection in patients with modified radical mastectomy: a prospective randomized study	• Study location Turkey • Study setting Department of General Surgery. • Study dates June 2006 and June 2009. • Duration of follow-up 6 months after surgery • Sources of funding Not specified.	• Gentamicin collagen sponge	• No antibiotics Group 2 underwent modified radical mastectomy without the application of the Gentacoll.	• SSI • Length of hospital stay

1 See appendix D for full evidence tables.

2 Quality assessment of clinical studies included in the evidence review

3 All studies included in the review were RCTs. The quality of the evidence was started at high.
4 A number of studies demonstrated unclear blinding of participants however these studies
5 were not downgraded in this domain. Studies were mainly downgraded for unclear random
6 sequence generation, allocation concealment and blinding of outcome assessment.

Studies included in the review classified infections using different criteria including the Centres for Disease Control and Prevention (CDC) SSI criteria. Studies which did not explicitly describe criteria used for the classification of infection were downgraded for serious indirectness.

Outcomes at a number of different follow-up periods were reported in the studies included. Studies which did not specify a follow-up period were downgraded for serious indirectness. In such studies the follow-up period was assumed be the postoperative phase.

See evidence tables in appendix E for quality assessment of individual studies and appendix G for full GRADE tables.

Economic evidence

Included studies

A literature search was conducted to identify cost–utility analyses comparing strategies for the intraoperative use of antibiotics or antiseptics prior to wound closure. Standard health economic filters were applied to a clinical search, returning a total of 1,344 citations. Following review of all titles and abstracts, 11 studies were identified as being potentially relevant to this decision problem, and were ordered for full review. After reviewing the full texts, 2 studies were included as economic evidence for nasal decontamination. Both evaluated the cost-effectiveness of antibiotic-impregnated bone cement for use in hip surgery.

Graves et al. (2016)

Graves et al. (2016) developed a lifetime economic model comparing 9 infection control strategies in total hip replacement (THR) surgery, comprising the use or absence of: systemic antibiotics, antibiotic-impregnated bone cement, and novel ventilation techniques. For the purpose of this review, strategies that are identical except for plain cement vs. antibiotic cement are relevant. Baseline deep infection rates were from a multicentre RCT of operating theatre ventilation (3.4% in 2.5 years). A cohort of 77,321 THR patients progressed through a daily 9-state Markov model, including the risk of a deep SSI (up to 1 year), followed by treatment with debridement, 1 or 2-stage revision, or permanent resection, and death. Time-dependent transition probabilities between states were calculated by linking data from 5 databases: NHS Hospital Episode Statistics, Office for National Statistics, SSI Surveillance Service, National Joint Registry, and NHS England patient-report outcome measures data. Mortality was captured using national UK life tables. Relative effectiveness was identified by a systematic review and mixed treatment comparison with meta-regression, containing 12 studies (6 RCTs) and 123,788 THRs. Probability ratios for deep SSI, compared with the reference treatment of no systematic antibiotics, plain cement and standard ventilation, ranges from 0.22 (best) to 0.61.

Costs included components of each intervention and of treatments following SSI. Plain cement was £68 per THR, with antibiotic-impregnated cement at £95. Utility values were not based on EQ-5D, and were informed by published evidence as the NHS England data did not capture quality of life specifically following SSI or subsequent treatment. All outcomes were discounted by 3% per year.

With no systemic antibiotics and conventional ventilation, antibiotic-impregnated cement generated 0.001 additional QALYs and saved £60 per patient. It was 96% likely to be cost-saving from 1,000 probabilistic model runs, and gained QALYs in 62% of runs. With systemic antibiotics, antibiotic cement generated 0.001 additional QALYs and saved £14 per patient. The value of antibiotic-impregnated cement was reduced significantly when both systemic antibiotics and laminar airflow ventilation were used, generating 0.0001 additional QALYs

and a higher cost of £26 per patient compared with plain cement. The resulting ICER is in excess of £300,000 per QALY gained.

Cummins et al. (2009)

Cummins et al. (2009) also evaluated the cost-effectiveness of antibiotic-impregnated bone cement, for use in primary hip arthroplasty in the US. A lifetime Markov model composed of 4 health states was developed, capturing the primary procedure, septic and aseptic revision, and death. Septic and aseptic revision rates were informed by the Norwegian Arthroplasty Registry (1987–2004), with a relative risk of septic revision using plain cement of 1.8 (p = 0.01), and 1.3 for aseptic revision (p = 0.02). While this is not randomised evidence, it represents a rich data source (22,170 procedures over 14 years) and included a Cox regression to account for heterogeneity between patients (e.g. use of systemic antibiotic prophylaxis, theatre characteristics, age and sex). Operative mortality was 0.23%, otherwise mortality was informed by national US life tables.

Direct costs included the primary procedure and acute hospitalisation, antibiotic-impregnated cement (+£422), septic revision (£67,500) and aseptic revision (£24,500), from various published sources. Utility inputs, loosely informed by a study using the SF-36 questionnaire, applied a 10% utility loss for aseptic revision and a 20% loss for a septic revision. All outcomes were discounted by 3% per year.

When only differences in septic revisions were included, antibiotic cement gained 0.009 QALYs and had an additional cost of £141 per patient, compared with plain cement, producing an ICER around £15,600 per QALY gained. When the observed effect of reducing the risk of aseptic revisions was also captured, antibiotic cement was found to be dominant. Results were found to be relatively sensitive to cost inputs, and to the age of the patient, being more likely to be cost-effective in younger patients who are at risk of revision for longer than older patients due to age-related mortality. However, these were evaluated against US cost-effectiveness benchmark of $50,000 (£35,000), which has limited applicability to the UK setting. Probabilistic analysis was not reported.

Excluded studies

Studies that were excluded upon full review are listed in Appendix J, including the primary reason for exclusion. Among the excluded studies is a cost–utility analysis by some of the authors of the included Graves et al. (2016) study, which used the same model structure and much of the same data but was in the Australian setting (Merollini et al., 2013). Inputs such as baseline infection rates and costs were therefore less applicable to the NHS setting. Its conclusions regarding antibiotic cement versus plain cement, alongside systemic antibiotics, were consistent with Graves et al. (2016). As such, this study was selectively excluded to avoid presenting the same evidence twice, in favour of only including the more applicable and more recent UK study.

Economic model

New economic modelling for this topic was not prioritised by the guideline development committee, therefore no model was developed.

Summary of studies included in the economic evidence review

A summary of the 2 studies included as economic evidence is provided below. Full economic evidence tables for each study are provided in Appendix H. A summary economic evidence profile is provided in Appendix I.

Evidence statements

The format of the evidence statements is explained in the methods in appendix B. Evidence statements were also stratified by follow up period and were formulated to reflect the surgical procedure and surgical wound classification.

Clinical evidence

Erythromycin and colistin loaded bone cement

Outcomes at 1 year after surgery

- Low to very low quality evidence from 1 RCT, including 2,948 knees, could not differentiate the following outcomes between people who received erythromycin and colistin loaded bone cement during total knee arthroplasty and those who received bone cement without antibiotic:
  - SSI
  - Superficial SSI
  - Deep SSI

Vancomycin powder

Outcomes at 3 months after surgery

- Very low quality evidence from 1 RCT, including 907 people, could not differentiate the following outcomes between people who received vancomycin powder before wound closure during spinal surgery and those who did not receive additional antibiotic powder:
  - SSI
  - Superficial SSI
  - Deep SSI.

  These results were also consistent in the following subgroups:

  - Instrumented spinal surgery
  - Non-instrumented spinal surgery

Ampicillin powder

Outcomes at 3 weeks after surgery

- Moderate quality evidence from 1 RCT, including 130 people, indicated that people who received ampicillin powder before wound closure during **appendectomy** had a lower incidence of SSI compared to those who received a placebo.

Topical cefotaxime

Outcomes at 1 month after surgery

- Very low quality evidence from 1 RCT, including 177 people, could not differentiate the following outcomes between people who received topical cefotaxime before wound closure during **abdominal surgeries** and those who did not receive topical antibiotic:
  - SSI
  - Septicaemia
  - Mortality post-surgery

These results were also consistent in the following subgroups:

- appendectomy
- biliary surgery
- colonic surgery
- drainage of intra-abdominal abscess

Topical cephaloridine

Outcomes at 1 month after surgery

- Moderate quality evidence from 1 RCT, including 401 people, indicated that people who received topical cephaloridine before wound closure had a lower incidence of SSI compared to those who did not receive topical antibiotic.

  This result was also consistent in the following subgroups:
  - clean surgery
  - contaminated surgery

Topical povidone iodine spray

Outcomes at 2 weeks after surgery

- Moderate quality evidence from 1 RCT, including 153 people, indicated that people who received topical povidone iodine spray before wound closure during **abdominal surgery** had a lower incidence of SSI compared to those who did not receive topical antiseptic spray.

- Moderate quality evidence from 1 RCT, including 153 people, could not differentiate postoperative antibiotic use between people who received topical povidone iodine spray before wound closure during **abdominal surgery** and those who did not receive topical antiseptic spray.

Outcomes at 1 month after surgery

- Moderate quality evidence from 2 RCTs, including 702 people, indicated that people who received topical povidone iodine spray before wound closure had a lower incidence of SSI compared to those who did not receive topical antiseptic spray.

  This result was also consistent in the following subgroups:
  - clean surgery
  - clean/contaminated surgery
  - contaminated surgery
  - dirty surgery

- Very low quality evidence from 1 RCT, including 100 people, could not differentiate SSI between people who received topical povidone iodine spray before wound closure during **appendectomy** and those who received ampicillin powder.

Povidone iodine solution

Outcomes during postoperative period

- Very low quality evidence from 1 RCT, including 107 people, could not differentiate SSI between people who received povidone iodine solution before wound closure during **gastric and colorectal surgery** and those who did not receive antiseptic solution.

2.5% Iodine in 70% ethanol

Outcomes at 2 weeks after surgery

- Low quality evidence from 1 RCT, including 662 people, could not differentiate SSI between people who received topical 2.5% iodine in 70% ethanol as well as drapes before wound closure during **caesarean section** and those who did not receive topical antiseptics.

- Low quality evidence from 1 RCT, including 678 people, could not differentiate SSI between people who received topical 2.5% iodine in 70% ethanol and no drapes before wound closure during **caesarean section** and those who did not receive topical antiseptics.

Gentamicin collagen sponge

Outcomes at 1 week after surgery

- Very low quality evidence from 2 RCTs, including 301 people, could not differentiate SSI between people who received gentamicin collagen sponge before wound closure and those who did not receive a gentamicin collagen sponge. This result was also consistent in abdominoperineal resection alone.
    - Very low quality from 1 RCT, including 200 people, indicated that people who received gentamicin collagen sponge before wound closure during **hidradenitis suppurativa surgery** had lower incidence of SSI compared to people who did not receive a gentamicin collagen sponge.

Outcomes at 2 weeks after surgery

- Very low quality evidence from 1 RCT, including 159 people, could not differentiate SSI between people who received gentamicin collagen sponge before wound closure during **pilonidal sinus surgery** and those who did not receive a gentamicin collagen sponge.

Outcomes at 1 month after surgery

- Low quality from 4 RCTs, including 1,063 people, could not differentiate SSI between people who received gentamicin collagen sponge before wound closure and those who did not receive a gentamicin collagen sponge. This result was also consistent in the following subgroups:
    - abdominoperineal resection
    - splenectomy
    - colorectal surgery
    - hip arthroplasty

- Low quality evidence from 2 RCTs, including 878 people, could not differentiate superficial SSI between people who received gentamicin collagen sponge before wound closure and those who did not receive a gentamicin collagen sponge. This result was also consistent in the following subgroups:
    - Hip arthroplasty
    - Colorectal surgery

- Low quality evidence from 2 RCTs, including 878 people, could not differentiate deep SSI between people who received gentamicin collagen sponge before wound closure and those who did not receive a gentamicin collagen sponge. This result was also consistent in hip arthroplasty alone.

- Moderate quality evidence from 2 RCTs, including 902 people, could not differentiate mortality post-surgery between people who received gentamicin collagen sponge before wound closure and those who did not receive a gentamicin collagen sponge. This result was also consistent in the following subgroups:
    - hip arthroplasty
    - colorectal surgery

- Moderate quality evidence from 1 RCTs, including 684 people, could not identify a difference in mean length of stay between people who received gentamicin collagen sponge before wound closure during **hip arthroplasty** and those who did not receive a gentamicin collagen sponge.

- Very low quality evidence from 2 RCTs, including 800 people, indicated that people who received gentamicin collagen sponge before wound closure had lower incidence of SSI compared to people who received a placebo. This result was also consistent in loop-ileostomy alone.
    - Very low quality evidence from 1 RCT, including 720 people, indicated that people who received gentamicin collagen sponge before wound closure during cardiac surgery had a lower incidence of SSI compared to those who received a placebo.

- Very low quality evidence from 3 RCTs, including 993 people, could not identify a difference in superficial SSI between people who received gentamicin collagen sponge before wound closure and those who received a placebo. This result was also consistent in the following subgroups:
    - loop-ileostomy
    - cardiac surgery
    - colorectal surgery

- Very low quality evidence from 3 RCTs, including 993 people, indicated that people who received gentamicin collagen sponge before wound closure had a lower incidence of deep SSI compared to those who received a placebo. This result was also consistent in cardiac surgery alone.
    - Low quality evidence from 1 RCT, including 80 people, could not identify a difference in deep SSI between people who received gentamicin collagen sponge before wound closure during **loop-ileostomy** and those who received a placebo

Outcomes at 2 months after surgery

- Very low quality evidence from 3 RCTs, including 2,649 people, could not differentiate SSI between people who received gentamicin collagen sponge before wound closure and those who did not receive a gentamicin collagen sponge. This result was also consistent in abdominoperineal resection alone.
    - High quality evidence from 1 RCT, including 1,950 people, indicated that people who received gentamicin collagen sponge before wound closure during **cardiac surgery** had a lower incidence of SSI

compared to those who did not receive a gentamicin collagen sponge.

- Moderate quality evidence from 1 RCT, including 602 people, indicated that people who did not receive a gentamicin collagen sponge before **colorectal surgery** lower incidence of SSI compared to those who did receive a gentamicin collagen sponge.

- Very low quality evidence from 3 RCTs, including 2,649 people, could not differentiate superficial SSI between people who received gentamicin collagen sponge before wound closure and those who did not receive a gentamicin collagen sponge. This result was also consistent in abdominoperineal resection alone.
  - High quality evidence from 1 RCT, including 1,950 people, indicated that people who received gentamicin collagen sponge before wound closure during **cardiac surgery** had a lower incidence of superficial SSI compared to those who did not receive a gentamicin collagen sponge.
  - Moderate quality evidence from 1 RCT, including 602 people, indicated that people who did not receive a gentamicin collagen sponge before **colorectal surgery** lower incidence of superficial SSI compared to those who did receive a gentamicin collagen sponge.

- Very low quality evidence from 3 RCTs, including 2,649 people, could not differentiate deep SSI between people who received gentamicin collagen sponge before wound closure and those who did not receive a gentamicin collagen sponge. This result was also consistent in the following subgroups:
  - abdominoperineal resection
  - cardiac surgery
  - colorectal surgery

- Moderate to low quality evidence from 1 RCT, including 602 people, could not differentiate the following outcomes between people who received gentamicin collagen sponge before wound closure during **colorectal surgery** and those who did not receive a gentamicin collagen sponge:
  - Organ space SSI
  - Hospital readmission

- Low quality evidence from 1 RCT, including 1,950 people, could not differentiate the following outcomes between people who received gentamicin collagen sponge before wound closure during **cardiac surgery** and those who did not receive a gentamicin collagen sponge:
  - Hospital mortality
  - Mortality post-surgery

Outcomes at 3 months after surgery

- Moderate quality evidence from 5 RCTs, including 2,473 people, could not differentiate SSI between people who received gentamicin collagen sponge before wound closure and those who did not receive a gentamicin collagen sponge. This result was also consistent in the following subgroups:
  - cardiac surgery
  - colorectal surgery

  - abdominoperineal resection
  - pilonidal sinus surgery

- Low quality evidence from 2 RCT, including 2,044 people, could not differentiate superficial SSI between people who received gentamicin collagen sponge before wound closure during **cardiac surgery** and those who did not receive a gentamicin collagen sponge.

- Very low quality evidence from 1 RCT, including 171 people, could not differentiate superficial/ deep SSI between people who received gentamicin collagen sponge before wound closure during **colorectal surgery** and those who did not receive a gentamicin collagen sponge.

- Low quality evidence from 2 RCT, including 2,044 people, could not differentiate deep SSI between people who received gentamicin collagen sponge before wound closure during **cardiac surgery** and those who did not receive a gentamicin collagen sponge.

- Moderate quality evidence from 2 RCT, including 2,044 people, could not differentiate organ/ space SSI between people who received gentamicin collagen sponge before wound closure during **cardiac surgery** and those who did not receive a gentamicin collagen sponge.

- Low quality evidence from 1 RCT, including 542 people, could not differentiate mortality post-surgery between people who received gentamicin collagen sponge before wound closure during **cardiac surgery** and those who did not receive a gentamicin collagen sponge.

- Low quality evidence from 1 RCT, including 1,502 people, could not differentiate hospital readmission between people who received gentamicin collagen sponge before wound closure during **cardiac surgery** and those who did not receive a gentamicin collagen sponge.

Outcomes at 6 months after surgery

- Low quality evidence from 2 RCTs, including 621 people, could not differentiate SSI between people who received gentamicin collagen sponge before wound closure and those who did not receive a gentamicin collagen sponge. This result was also consistent in the following subgroups:
  - prosthetic repair of groin hernias
  - abdominoperineal resection

- Moderate quality evidence from 1 RCT, including 44 people, indicated that people who received gentamicin collagen sponge before wound closure during **abdominoperineal resection** had a shorter mean length of hospital stay compared to those who did not receive a gentamicin collagen sponge.

Outcomes during postoperative phase

- Low quality evidence from 1 RCT, including 221 people, indicated that people who received gentamicin collagen sponge before wound closure during **colorectal surgery** had lower incidence of SSI compared to people who did not receive a gentamicin collagen sponge.

Economic evidence

Antibiotic-impregnated bone cement

- Two partially applicable cost–utility analyses with potentially serious limitations compared antibiotic-impregnated bone cement with plain bone cement for use in primary **hip replacement surgery**. A UK study found that antibiotic cement is likely to be dominant, unless its benefit is eroded by the presence of other infection control interventions such as a combination of systemic antibiotics and laminar airflow theatre ventilation. A US study found that antibiotic cement is dominant if its effect on all types of hip revision are considered, but its ICER is around £16,000 per QALY gained if only septic revisions are considered.

Recommendations

C.1 Only apply an antiseptic or antibiotic to the skin before wound closure as part of a clinical research trial.

C2. Consider using gentamicin-collagen implants in cardiac surgery.

Research recommendations

1. Is the application of antiseptics and antibiotics in the operative field before wound closure, clinically and cost effective in reducing surgical site infection rates?

Rationale and impact

Why the committee made the recommendations

Limited evidence was identified on the intraoperative use of antiseptics before wound closure. Although this evidence suggested that topical povidone-iodine was effective in reducing surgical site infections, the studies were dated. This evidence also suggested that topical antiseptics, such as iodine in alcohol solution, are not effective in reducing surgical site infections.

The evidence on topical antibiotics before wound closure was varied, but also included several older studies. Some studies showed that antibiotics, such as ampicillin powder and cephaloridine, reduced the number of surgical site infections. However, the evidence for other antibiotics, such as vancomycin, which is widely used worldwide and commonly used in cardiac, orthopaedic and spine surgery, suggested no reduction in surgical site infections.

The committee agreed that the evidence was not current or clear enough to make a recommendation on the use of topical antiseptics and antibiotics before wound closure. The committee also took into account concerns about antimicrobial resistance and the potential of multidrug resistance, and agreed that without new conclusive evidence, use of intraoperative topical antibiotic and antiseptics should be stopped. They agreed that this is an important area for further research and recommended that they should be considered only in the context of further research to help limit unnecessary use and determine their clinical effectiveness. They also developed a research recommendation to determine the clinical and cost effectiveness of applying antiseptics and antibiotics before wound closure.

There was some economic evidence that showed antibiotic loaded bone cement was cost effective compared with plain cement. However, the committee were not confident that the evidence was applicable to current NHS practice. In addition, the clinical evidence suggested that antibiotic loaded bone cement did not reduce the number of surgical site infections. The committee agreed that the evidence was too limited to make a recommendation for this intervention.

Evidence was also identified on the use of gentamicin implants before skin closure during different surgical procedures. In particular, the evidence suggested that gentamicin-collagen implants reduced the incidence of surgical site infections at 1 month and 2 months in people having cardiac surgery. Although the evidence was limited, cardiac surgery is associated with a high risk of surgical site infection. Therefore, the committee agreed that gentamicin implants should be an option to reduce the risk of infection.

Impact of the recommendations on practice

In practice, the use of topical antiseptics and antibiotics before wound closure varies. Limiting their use to clinical trials is likely to reduce their misuse in practice and encourage research in this area.

Currently, gentamicin-collagen implants are considered best practice in cardiac surgery, however not all centres currently use them. The new recommendation may help to reduce variation and standardise practice. Any resource impact is likely to be balanced by savings from a reduction in the number of surgical site infections.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee identified SSI including superficial SSI, deep SSI and organ space SSI as outcomes of interests. Studies included in the review captured outcomes at a number of different follow up periods. Furthermore, 2 studies were identified [Andersson 2010 and Collins 201], that reported outcomes at various time points during the study period. Due to this, data was stratified based on different follow up periods. While the committee took into all the outcomes at different follow up periods into consideration, based on the CDC definition of SSI, the committee identified outcomes up to 30 days and 1 year to be important.

The quality of the evidence

Overall, the committee noted that the studies ranged from moderate to very low quality evidence. Study locations also varied, with 5 studies being identified, which were conducted in the UK. Furthermore, studies also ranged in sample sizes. The largest evidence base was identified for gentamicin collagen implants and sample sizes ranged from 50 participants to 1,950 participants.

The committee noted that a number of studies included in the review were conducted before the year 2000. Furthermore, majority of the evidence identified for 2.5% iodine in 70% alcohol [Cordtz 1989] cephaloridine [Evans 1974], povidone iodine [Sherlock 1984, Gray 1981, Walsh 1981 and Parker 1985], cefotaxime [Moesgaard 1989] and ampicillin [Rickett 1969] were conducted before the 1990s. The committee discussed that practice is too far removed from the time these studies were conducted. Furthermore, products such as cephaloridine can no longer be found on the market. Therefore, with no new evidence for these interventions, the committee could not make recommendations based on outdated evidence.

Studies included in the review classified surgical site infections using different criteria. Ten studies were identified which classified surgical site infections based on the Centres of Disease Control and Prevention (CDC) criteria. A number of studies were identified which based the classification of surgical site infections on purulent discharge with and without the inclusion of bacteriological confirmation. Nine studies were found which did not define criteria used for the classification on infections. These studies were downgraded for serious

indirectness, as it was unclear if these infections were classified in a similar manner to the other included studies.

During committee discussions, the importance of identifying surgical site infections up to 30 days after surgery and 1 year after orthopaedic surgery were discussed. In this review, evidence on outcomes at different follow up periods post-surgery were identified. In order to adequately assess the outcomes, data was stratified based on follow up period. However, 2 studies [Harihara 2006 and Rutten 1997] included in the review did not state the period in which the outcomes were followed up. For the purpose of this review, it was assumed that these studies followed up outcomes during the postoperative phase. However, as follow up was unclear, these studies were downgraded for serious indirectness.

Benefits and harms

It was discussed that surgical site infections result in poor patient outcomes and increased costs. In terms of the use of gentamicin sponges, 19 studies were identified which explored the use of the sponges in a number of different types of surgery. Evidence demonstrated that the gentamicin implants were effective in cardiac surgery which is considered a high risk surgery. Therefore, it was noted that the use of gentamicin collagen implants may aid in reducing the risk of infection in people undergoing cardiac surgery.

As part of this review, adverse events such as kidney toxicity and anaphylaxis were examined. No studies were identified which explored these outcomes. It was noted that nephrotoxicity is a side effect with the use of all aminoglycosides. In adults, it occurs more commonly in the elderly and also occurs most commonly in children with renal failure. The committee discussed this potential harm and noted that manufacturers of the gentamicin collagen implants state that the use of the implants is associated with low systemic rates of the antibiotic.

The committee also discussed that studies involving the use of gentamicin collagen implants tend to not include patients with reduced renal function, therefore it is difficult to ascertain side effects associated with the use of the implants in this patient population. However, the committee noted that caution must be taken when considering use of the implants in people with poor renal function. Furthermore, the research recommendation developed also includes organ toxicity as an important outcome of interest.

Antimicrobial resistance is a major concern with the use of antibiotics and antiseptics. The committee discussed that during surgery, along with receiving skin antiseptics, people may also receive additional peri-operative antimicrobial prophylaxis as part of the standard protocol. This raises the risk of multidrug resistance and it also means that identifying antimicrobial resistance to a single intervention is difficult.

Based on the evidence, the committee recommended gentamicin collagen implants to be considered in cardiac surgery. However, no evidence was identified that which examined the antimicrobial resistance associated with the use of these implants. Additionally, as the evidence on other antiseptics and antibiotics were poor, the committee made an additional recommendation for the use of antiseptics and antibiotics to only be considered as part of a clinical trial.

While this recommendation should reduce the misuse of these interventions and in turn reduce the risk of antimicrobial resistance, the committee noted that more evidence is required to examine the risk of antimicrobial resistance. Therefore, the committee made a research recommendation to further examine the effectiveness intraoperative antiseptics and antibiotics, in which antimicrobial resistance is an important outcome.

Cost effectiveness and resource use

The committee discussed the 2 published cost-effectiveness analyses identified in the economic literature review. Both studies evaluated the use of antibiotic-impregnated bone cement for use during total hip replacement, compared with using plain bone cement. The UK study (Graves et al., 2016) found in favour of antibiotic bone cement, unless there were other infection control measures in place; namely, antibiotic prophylaxis and laminar airflow theatre ventilation. The committee advised that laminar airflow is routinely used in orthopaedic surgery in the NHS, and antibiotic prophylaxis use is not uncommon, such that it is unclear whether the Graves et al. study provides evidence that antibiotic-impregnated bone cement is cost effective. Further, the committee advised that it is routine practice to avoid using bone cement in primary joint replacement surgery, if possible; therefore, even the UK study might have limited applicability to the NHS setting. The committee also agreed that the clinical evidence underpinning both models is of insufficient quality to support recommendations regarding antibiotic-impregnated bone cement. The Graves et al. study was based on a network meta-analysis of 12 studies, of which 6 were RCTs; however, none of the RCTs compared antibiotic-impregnated bone cement with plain bone cement. This comparison was therefore informed by direct observational studies and indirect evidence from the wider network, which the committee agreed was weak evidence to inform an economic evaluation. The second study (Cummins et al., 2009) was agreed to be less applicable to NHS practice, being a US analysis based on long-term Norwegian registry data. Although an attempt had been made to account for potential confounding factors in the clinical evidence, the committee agreed that this is weak evidence to inform an economic evaluation.

The committee discussed the use of gentamicin-collagen sponges in cardiac surgery. It agreed that the most compelling evidence for the effectiveness of gentamicin-collagen sponges is in cardiac surgery, and noted that the original CG74 committee also made this comment. However, no cost-effectiveness evidence regarding their use was identified. The committee advised that the cost of gentamicin-collagen sponges vary by hospital, ranging from around £20 to £90 per sponge. The committee estimated that around 25,000 cardiac surgery procedures occur annually in the NHS; therefore, the use of gentamicin-collagen sponges in all cardiac surgery would have resource implications. If the typical cost per sponge is £55 – the midpoint of the committee's range – this would imply a resource impact of £1,375,000; however, the committee advised that these sponges are often used in NHS cardiac surgery already, as they are perceived to reflect best practice. If they are already in use the resource impact of full adoption would be lower that the above figure; for example, £962,500 if they are currently used in 30% of cardiac surgery procedures. This resource impact estimate does not capture cost savings associated with a reduction in the incidence of SSI that would occur as a result of using gentamicin-collagen sponges. A UK hospital SSI surveillance study (Jenks et al., 2014) estimated a mean SSI cost of £11,003 in cardiac surgery patients, higher than SSIs in most other surgical categories. Avoiding 91 SSIs across 25,000 annual cardiac surgical procedures would therefore save £1 million in SSI treatment costs. Based on the economic model developed for this guideline evaluating nasal decontamination of *S. aureus,* the committee was aware that infection control tends to be cost-effective, particularly when the cost impact of a SSI is high, like in the case of cardiac surgery. The committee was therefore satisfied that a recommendation to consider the use of gentamicin-collagen sponges in cardiac surgery, where its clinical evidence is the most supportive, is likely to be a cost-effective used of NHS resources.

Other factors the committee took into account

The number of studies identified for each intervention varied. While single studies were found which explored the clinical effectiveness of antibiotic loaded bone cement, 2.5% iodine in 70% alcohol, cefotaxime, cephaloridine, ampicillin and vancomycin, 5 studies explored the

effectiveness of povidone iodine and 19 studies investigated the effectiveness of gentamicin collagen implants. These studies also explored a number of different surgery types.

Studies examining the effectiveness of povidone iodine mainly involved people undergoing abdominal procedures such as gastric surgery and colorectal surgery. While topical povidone iodine did demonstrate a significant reduction in SSI at 2 weeks in people undergoing abdominal surgery, no significant results were identified in people undergoing various clean, contaminated or dirty abdominal procedures.

Studies examining the effectiveness of gentamicin collagen implants included people undergoing cardiac, colorectal and hidradenitis suppurative surgery as well as arthroplasty, pilonidal sinus excision, prosthetic repair of groin hernias, abdominoperineal resection, mastectomy and loop-ileostomy. Gentamicin collagen implants demonstrated a significant reduction in SSIs at 1 week after surgery in people undergoing hidradenitis suppurativa surgery as well as a reduction in SSIs at 1 month and 2 months after surgery in people undergoing cardiac surgery.

Conflicting data was identified on the clinical effectiveness of the implants in people undergoing colorectal surgery. Two studies [Nowacki 2006 and Pochhammer 2015] were identified which demonstrated a non-significant reduction in SSIs, as well as superficial SSIs, in people under colorectal surgery. One partially applicable study [Rutten 1997] further demonstrated a significant reduction in SSIs. However, one study [Bennett-Gurerro 2010 a] demonstrated a significant risk of SSI at 2 months associated with the use of gentamicin implants in people undergoing colorectal surgery.

The authors of the paper did hypothesis that the presence of sponge mass may have created a mechanical barrier to early wound healing that promoted infection, however such significant results were not replicated in any other study identified. Furthermore, the study which demonstrated a significant reduction had a small sample size and did not state the follow-up period. Due to the lack of conclusive evidence on the use of gentamicin collagen implants in colorectal surgery, no recommendations were made for this surgery type.

The committee noted that the application of antiseptics and antibiotics vary. While gentamicin collagen sponges are implanted into the wound cavity for the purpose of wound disinfection, topical antiseptics are generally used for skin re-disinfection. Antibiotics can also be applied topically, but usually in the form of powders, as reflected in the evidence identified. The committee wanted to make a clear distinction between wound disinfection and skin re-disinfection. With regards to wound disinfection, evidence was mainly identified for the use of gentamicin collagen implants. Based on the evidence identified the committee recommended for the gentamicin collagen implants to be considered in cardiac surgery.

No new evidence was identified which demonstrated the clinical effectiveness of skin re-disinfection using antiseptics before would closure in reducing the incidence of SSI. Due to the lack of evidence, the committee discussed the need for further research. Therefore, no recommendations were made for the use of antiseptic in practice, but a research recommendation was made to promote further research.

Questions were also raised on the availability of interventions. Evidence was identified which suggested that cephaloridine demonstrated a significant reduction in SSIs in people undergoing contaminated surgeries. However, the committee noted that while this intervention is effective, this product is no longer available on the market.

Additionally, it was noted that studies included in the review did not provide evidence on children. Due to the lack of evidence in this population, specific recommendations for children could not be made. Caution must be taken when considering use in children with renal failure.

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Appendices

Appendix A – Review protocols

Review protocol for application of intraoperative antiseptics and antibiotics before wound closure.

ID	Field	Content
0.	PROSPERO registration number	[Complete this section with the PRSOSPERO registration number once allocated]
1.	Review title	Application of intraoperative topical antiseptics and antibiotics before wound closure.
2.	Review question	RQ3: Is the application of antiseptics and antibiotics in the operative field before wound closure clinically effective in reducing surgical site infection rates?
3.	Objective	Evaluate the effectiveness of the application of intraoperative antiseptics and antibiotics to the operative field before wound closure in the prevention of SSI.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Cumulated Index to Nursing and Allied Health Literature (CINAHL) • Database of Abstracts of Reviews of Effectiveness (DARE) • Embase

		• MEDLINE/MEDLINE in Process • ClinicalTrials.gov • Current Controlled Trials • United Kingdom Clinical Research Network's (UKCRN) Portfolio Database • NHS EED Searches will be restricted by: • No date limit applied • English language • Human studies Other searches: • Reference searching • Inclusion lists of systematic reviews Full search strategies for all databases will be published in the final review.
5.	Condition or domain being studied	Surgical site infection is a type of health-care associated infection in which a wound infection occurs after an invasive procedure. Surgical site infections have been shown to compose up to 20% of all of healthcare-associated infections. At least 5% of patients undergoing a surgical procedure develop a surgical site infection.
6.	Population	Inclusion: People of any age undergoing surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery)

		Exclusion: Patients undergoing a surgical procedure that does not involve a visible incision, and therefore does not result in the presence of a conventional surgical wound.
7.	Intervention/Exposure/Test	• Different antibiotic classes used alone or included in bone cement during orthopaedic surgery (penicllins, cephalosporins, fluoroquinolones, aminoglycosides, monobactams, carbopanems, macrolides and vancomycin) • Gentamicin collagen sponges, beads and gel • Cefotaxime • Chlorhexidine • Iodine • Iodophors including povidone iodine.
8.	Comparator/Reference standard/Confounding factors	• No skin antiseptics/ antibiotics • Different antiseptics/ antibiotics • Placebo
9.	Types of study to be included	• RCTs • Systematic reviews of RCTs • If less than 5 RCTs identified, quasi randomised trials will be used.
10.	Other exclusion criteria	• Conference abstracts and non-published studies will be excluded from the review. • Non-English language publications

11.	Context	Surgical site infection: prevention and treatment was published in October 2008. This guideline includes recommendations on information for patients and carers, the preoperative phase, the intraoperative phase and the post-operative phase. The guideline underwent regular surveillance at 3, 6 and 8 years following publication. During the 8 year surveillance process new evidence on the application of intraoperative topical antiseptics and antimicrobials before wound closure was identified. This warranted an update of this review question. It became apparent during the development of the update of the question carried forward from the original guideline that antibiotics should be included in the question. Also, the term 'topical' should be changed to 'operative field'. This decision was based on the committee input during the development of the review protocol. Hence, the review question answered in this update is: Is the application of antiseptics and antibiotics in the operative field before wound closure clinically effective in reducing surgical site infection rates?
12.	Primary outcomes (critical outcomes)	Surgical site infection (including SSIs up to 30 days and 1 year) defined using appropriate criteria such as CDC SSI criteria.
13.	Secondary outcomes (important outcomes)	• Mortality post-surgery • Length of hospital stay • Postoperative antibiotic use. • Infectious complications such as septicaemia or septic shock

		• Adverse events:
		  ○ Antimicrobial resistance
		  ○ Kidney toxicity
		  ○ Anaphylaxis

14.	Data extraction (selection and coding)	See Appendix B
15.	Risk of bias (quality) assessment	See Appendix B
16.	Strategy for data synthesis	See Appendix B
17.	Analysis of sub-groups	• Primary closure • Delayed closure • Type of surgery (including cardiac and orthopaedic surgery) • Wound classification (clean, clean-contaminated, contaminated, dirty) • Elective surgery • Emergency surgery
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic

		☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	April 2018		
22.	Anticipated completion date	April 2019		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☐
		Piloting of the study selection process	☑	☐

		Formal screening of search results against eligibility criteria	☑	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail** SSI@nice.org.uk **5c Named contact address** NICE Guideline Updates Team Centre for Guidelines		

		NICE 10 Spring Gardens London, SW1A 2BU] **5d Named contact phone number** +44 (0) 300 323 0410 **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and NICE Guideline Updates Team
25.	Review team members	From the Centre for Guidelines: • Caroline Mulvihill, Guideline Lead • Shreya Shukla, Technical Analyst • Jamie Elvidge, Health Economist • Sarah Glover, Information Specialist
26.	Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.

28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are: Chair: Damien Longson Members: • Melanie Burden, Infection Control Nurse • Pamela Carroll, Theatre Practitioner • Annie Hitchman, Patient/ carer • Peter Jenks, Microbiologist • David Leaper, Surgeon • Thomas Pinkney, Surgeon • Melissa Rochon, Infection Control Nurse • Giovanni Satta, Microbiologist • David Saunders, Anaesthetist Nigel Westwood, Patient/ carer
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	The reviewers and guideline committee work with NICE's communications team to disseminate and promote awareness of the guideline at the time of publication and afterwards.

		Members from the NICE communications team discuss with the reviewers and the committee opportunities for promoting the guideline. Committee members may be asked to take part in such activities. With help from the guideline committee and the developer, they identify how to reach relevant audiences for the guideline, including people using services, carers, the public, practitioners and providers. NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. NICE may also use other means of raising awareness of the guideline – for example, newsletters, websites, training programmes, conferences, implementation workshops, NICE field team support and other speaking engagements. Some of these may be suggested by guideline committee members (particularly members affiliated to organisations for people using services and carer organisations). Each guideline is different and activities for raising awareness will vary depending on the type and content of the guideline.
32.	Keywords	Surgical site infections, superficial SSI, deep SSI, deep organ space SSI, antiseptics, antibiotics, prevention, wound closure, Gentamicin collagen sponges, Cefotaxime, Chlorhexidine, Iodine, Iodophors, bone cement

33.	Details of existing review of same topic by same authors	N/ A – this is a new review
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	
36.	Details of final publication	www.nice.org.uk

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Appendix B- Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline.
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table . When systematic reviews were used as a source of primary data, any unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted

from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 3: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs were quality assessed using the Cochrane Risk of Bias Tool. Other study were quality assessed using the ROBINS-I tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis.

Fixed- and random-effects models (der Simonian and Laird) where appropriate, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

No MIDs were identified. Therefore, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings. In

particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 4.

Table 4: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the

GRADE criteria	Reasons for downgrading quality
	line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes were downgraded 1 level if presented as difference in medians without measure of spread. Evidence was further downgraded 1 level if the outcome was not statistically significant. Outcomes were downgraded 2 levels if effect size could not be calculated. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

Evidence statements for pairwise intervention data are classified in to one of four categories:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence could not demonstrate a meaningful difference.
- Situations where the data are consistent, at a 95% confidence level, with an effect in either direction (i.e. one that is not 'statistically significant') but the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect, evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 1.

Table 1 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 2.

Table 2 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness

Level	Explanation
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions were made on this basis, this is noted in the relevant section.

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

Databases	Date searched	Version/files
Cochrane Central Register of Controlled Trials (CENTRAL)	03/05/2018	Issue 3 of 12, March 2018
Cochrane Database of Systematic Reviews (CDSR)	03/05/2018	Issue 5 of 12, May 2018
Database of Abstracts of Reviews of Effect (DARE)	03/05/2018	Issue 2 of 4, April 2015
HTA	03/05/2018	Issue 4 of 4, October 2016
Embase (Ovid)	03/05/2018	1974 to 2018 May 02
MEDLINE (Ovid)	03/05/2018	1946 to Present with Daily Update
MEDLINE In-Process (Ovid)	03/05/2018	May 02, 2018
MEDLINE Epub Ahead of Print[a]	03/05/2018	May 02, 2018
CINAHL Plus with full text (EBSCO)	03/05/2018	-
MHRA – Drug Safety Alerts	03/05/2018	-

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases listed. The aim of the search was to identify evidence for the clinical question being asked. Randomised Controlled Trial and Systematic Review filters were used to identify the study designs specified in the Review Protocol.

1 Surgical Wound Infection/
2 Wound Infection/
3 SURGICAL WOUND DEHISCENCE/
4 Infection Control/
5 (infection adj4 control).tw.
6 Postoperative Complications/
7 ((wound? or incision* or suture*) adj4 (infect* or sepsis or septic* or dehiscen* or site* or contamin* or disrupt* or rupture* or separat*)).tw.
8 (SSI or SSIs or SSTI or SSTIs).tw.
9 Bacterial Infections/pc [Prevention & Control]
10 exp Specialties Surgical/
11 exp Surgical Procedures, Operative/
12 surgery.fs.
13 (surger* or surgical* or operat* or procedure*).tw.

14 exp Minimally Invasive Surgical Procedures/
15 (arthroscopy* or laparoscop* or thoracoscop* or endoscop*).tw.
16 or/1-15
17 exp Anti-Infective Agents, Local/
18 Iodine/ or Iodine Compounds/
19 iodine*.tw.
20 ((iod or iodide) adj4 derivative*).tw.
21 (iodinated adj4 compound*).tw.
22 (bioiodine or steribath or thysat or estroven or nasciodine or tcp).tw.
23 iodophor*.tw.
24 Povidone-Iodine/
25 ((povidone adj4 iodine) or povidone-iodine).tw.
26 ((povidine adj4 iodine) or povidine-iodine).tw.
27 (PVP-I or PVPI or PVP I or PVP-iodine or PVPiodine or pvp iodine or polyvinylpyrrolidoneiodine* or polyvinylpyrrolidone-iodine* or polyvinylpyrrolidone iodine*).tw.
28 (alphadine* or betadine* or betaisodona or betasept or "brush off" or "cold sore lotion" or disadine* or inadine or pharmadine* or povidine* or "savlon dry" or videne or codella).tw.
29 (octenisan or octenide or octenidine).tw.
30 Chlorhexidine/
31 chlorhexidine.tw.
32 (novalsan or tubulicid or "sebidan a" or mk 412a or mk-412a or mk412a).tw.
33 (acriflex or bacticlens or bactigras or "cx powder" or cepton or chlorasept or chlorohex or clorhexitulle or corsodyl or curasept or dispray or eczmol or elgydium or hibidil or hibiscrub or hibitane or hydrex or periochip or perioguard or rotersept or savlon or serotulle or spotoway or sterexidine or steripod or gluconate or uniscrub or unisept or "uriflex c" or phiso-med or CB12 or cetriclens or chloraprep or Clearasil or covonia or cyteal or dermol or eludril or germolene or germoloid* or hibi or hibicet or hibisol or instillagel or medi-swab or medi-wipe or mycil or nystaform* or quinoderm or savloclens or savlodil or sterets or steriwipe or tisept or torbetol or travasept or tri-ac or xylocaine).tw.
34 Disinfection/
35 exp Detergents/
36 exp Anti-Bacterial Agents/ or Antibiotic Prophylaxis/
37 (antimicrob* or anti microb* or antibiotic* or anti biotic*).tw.
38 ((anti-infective* or antiinfective* or antibacterial* or anti-bacteria*) adj (agent* or drug*)).tw.
39 microbicide?.tw.
40 (bacteriocide? or bacteriocidal agent?).tw.
41 carbapenem*.tw.
42 exp Carbapenems/
43 exp Cephalosporins/
44 cephalosporin*.tw.
45 exp Cephamycins/
46 (cephamycin* or cefoxitin*).tw.
47 exp Monobactams/
48 monobactam*.tw.
49 exp Penicillins/
50 Penicillin*.tw.
51 exp Thienamycins/
52 Thienamycin*.tw.
53 exp Macrolides/

54 macrolide*.tw.
55 exp Fluoroquinolones/
56 Fluoroquinolone*.tw.
57 exp Sulfonamides/
58 Sulfonamide*.tw.
59 exp Tetracyclines/
60 Tetracycline*.tw.
61 exp Aminoglycosides/
62 Aminoglycoside*.tw.
63 Clindamycin/
64 (Clindamycin* or dalacin* or zindaclin or duac or refobacin or treclin).tw.
65 exp Nitroimidazoles/
66 Nitroimidazole*.tw.
67 exp Gentamicins/ or Cefuroxime/ or Metronidazole/ or exp Ciprofloxacin/ or Vancomycin/
68 (gentamicin* or cidomycin or garamycin or genticin or lugacin or collatemp or gentisone or palacos or refobacin or septocoll or septopal or vipsogal or cefuroxime* or aprokam or ximaract or zinacef or zinnat or metronidazole* or acea or anabact or elyzol or flagyl or metrogel or metrolyl or metrosa or metrotop or metrozol or nidazol or noritate or norzol or rosiced or rozex or vaginyl or zadstat or zidoval or zyomet or entamizole or helimet or ciprofloxacin* or cetraxal or ciloxan or ciproxin or cilodex or vancomycin* or vancocin).tw.
69 Antisepsis/
70 (antiseptic? or antisepsis).tw.
71 or/18-70
72 exp Skin/
73 skin.tw.
74 administration, topical/ or administration, cutaneous/
75 (skin or topical* or cutan* or dermal* or dermis* or local* or cutis or derma or epicutaneous).tw.
76 (transcutan* or percutan* or cutan*).tw.
77 Surgical wound/
78 (wound* or incision*).tw.
79 or/72-78
80 ((before or prior to or previous to or preced*) adj4 (clos* or stitch* or stapl*)).tw.
81 (pre closure or preclosure or pre sutur* or presutur* or pre-suture*).tw.
82 Intraoperative care/ or Intraoperative Period/
83 (intraop* or intrawound*).tw.
84 or/80-83
85 71 and 79
86 17 or 85
87 16 and 86
88 84 and 87
89 (collagen adj4 (implant* or sponge* or bead* or gel*)).tw.
90 Surgical Sponges/ or Drug Implants/
91 Powders/
92 powder*.tw.
93 exp Bone Cements/
94 (bone adj4 cement*).tw.
95 or/89-94
96 16 and 71 and 95

97 88 or 96
98 animals/ not humans/
99 97 not 98
100 limit 99 to english language
101 Randomized Controlled Trial.pt.
102 Controlled Clinical Trial.pt.
103 Clinical Trial.pt.
104 exp Clinical Trials as Topic/
105 Placebos/
106 Random Allocation/
107 Double-Blind Method/
108 Single-Blind Method/
109 Cross-Over Studies/
110 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
111 (random$ adj3 allocat$).tw.
112 placebo$.tw.
113 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
114 (crossover$ or (cross adj over$)).tw.
115 or/101-114
116 Meta-Analysis.pt.
117 Network Meta-Analysis/
118 Meta-Analysis as Topic/
119 Review.pt.
120 exp Review Literature as Topic/
121 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
122 (review$ or overview$).ti.
123 (systematic$ adj5 (review$ or overview$)).tw.
124 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.
125 ((studies or trial$) adj2 (review$ or overview$)).tw.
126 (integrat$ adj3 (research or review$ or literature)).tw.
127 (pool$ adj2 (analy$ or data)).tw.
128 (handsearch$ or (hand adj3 search$)).tw.
129 (manual$ adj3 search$).tw.
130 or/116-129
131 115 or 130
132 100 and 131

Economic evaluations and quality of life data

Search filters to retrieve economic evaluations and quality of life papers were appended to the strategy listed above to identify relevant evidence. The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in MEDLINE in Process, Embase, The Cochrane Library, CINAHL and Econlit databases.

Sources searched to identify economic evaluations:

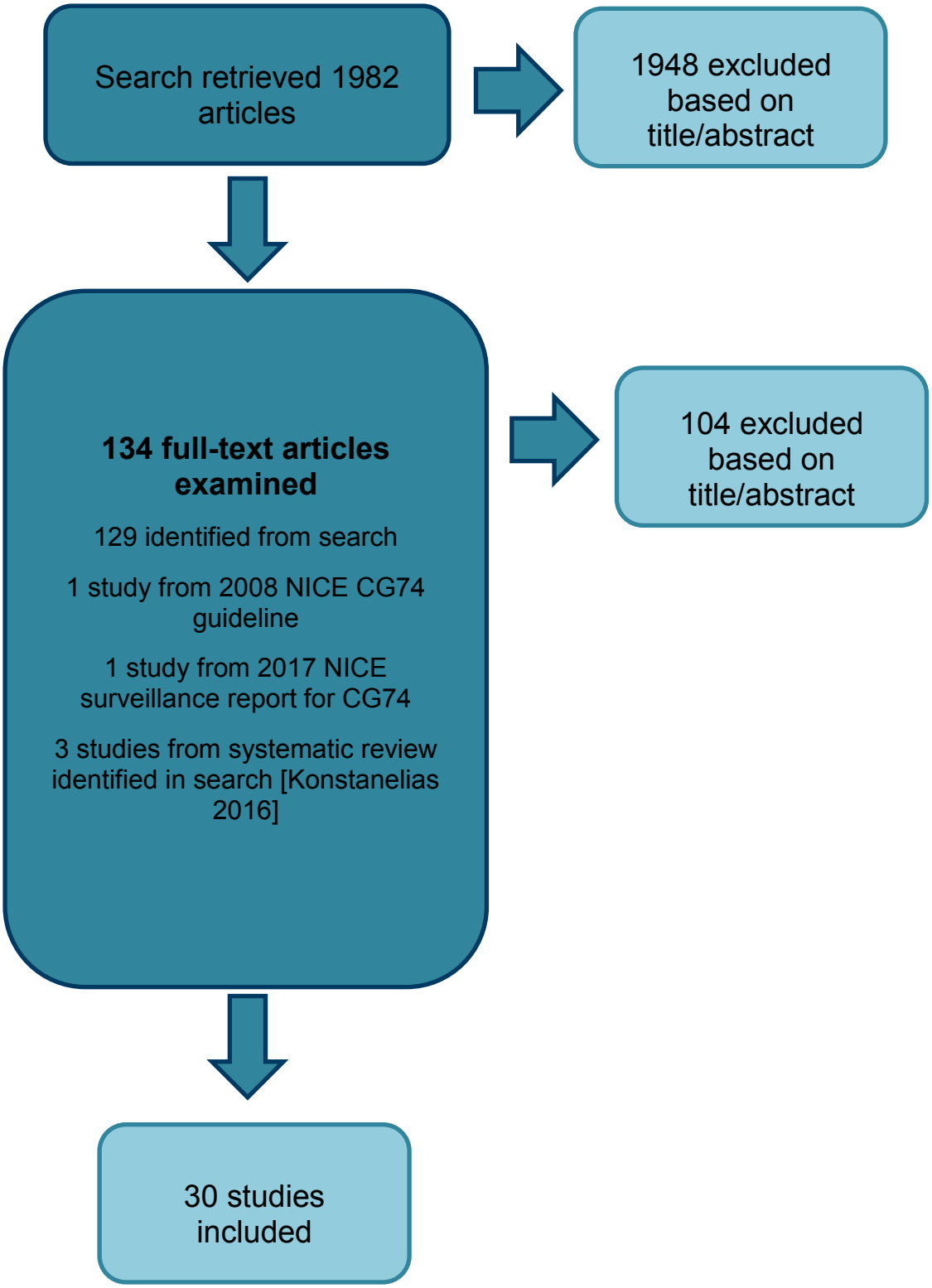
Databases	Date searched
Embase (Ovid)	04/05/2018
MEDLINE (Ovid)	04/05/2018
MEDLINE In-Process (Ovid)	04/05/2018
EconLit (Ovid)	04/05/2018
NHS Economic Evaluation Database (NHS EED) (legacy database)	04/05/2018
Health Technology Assessment (HTA Database)	04/05/2018
CINAHL Plus with Fulltext (EBSCO)	04/05/2018

Economic evaluations
1. Economics/
2. exp "Costs and Cost Analysis"/
3. Economics, Dental/
4. exp Economics, Hospital/
5. exp Economics, Medical/
6. Economics, Nursing/
7. Economics, Pharmaceutical/
8. Budgets/
9. exp Models, Economic/
10. Markov Chains/
11. Monte Carlo Method/
12. Decision Trees/
13. econom$.tw.
14. cba.tw.
15. cea.tw.
16. cua.tw.
17. markov$.tw.
18. (monte adj carlo).tw.
19. (decision adj3 (tree$ or analys$)).tw.
20. (cost or costs or costing$ or costly or costed).tw.
21. (price$ or pricing$).tw.
22. budget$.tw.
23. expenditure$.tw.
24. (value adj3 (money or monetary)).tw.
25. (pharmacoeconomic$ or (pharmaco adj economic$)).tw.

26. or/1-25

Quality of Life
1. "Quality of Life"/
2. quality of life.tw.
3. "Value of Life"/
4. Quality-Adjusted Life Years/
5. quality adjusted life.tw.
6. (qaly$ or qald$ or qale$ or qtime$).tw.
7. disability adjusted life.tw.
8. daly$.tw.
9. Health Status Indicators/
10. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15. (euroqol or euro qol or eq5d or eq 5d).tw.
16. (qol or hql or hqol or hrqol).tw.
17. (hye or hyes).tw.
18. health$ year$ equivalent$.tw.
19. utilit$.tw.
20. (hui or hui1 or hui2 or hui3).tw.
21. disutili$.tw.
22. rosser.tw.
23. quality of wellbeing.tw.
24. quality of well-being.tw.
25. qwb.tw.
26. willingness to pay.tw.
27. standard gamble$.tw.
28. time trade off.tw.
29. time tradeoff.tw.
30. tto.tw.
31. or/1-30

Appendix D – Clinical evidence study selection



Appendix E – Clinical evidence tables

E.1 Andersson 2010

	Andersson (2010)
Title	Local administration of antibiotics by gentamicin-collagen sponge does not improve wound healing or reduce recurrence rate after pilonidal excision with primary suture: a prospective randomized controlled trial
Study details	**Study type** • Randomised controlled trial • **Study location** Sweden • **Study setting** Multicentre (performed across 11 hospitals) • **Study dates** March 2013 to November 2005 • **Duration of follow-up** Up to 3 months • **Sources of funding** Not reported **Inclusion criteria** • Patients undergoing elective surgery for symptomatic pilonidal disease were included **Exclusion criteria** • None reported • **Sample size** n = 161 participants **Sample characteristics** • Split between study groups Intervention group = 83

	Andersson (2010)
	comparator group = 78 • **Loss to follow-up** 1 participant in each group did not receive the allocated intervention because their surgical wound was too large for suture • **%female** intervention group: 20% comparator group: 14% • **Median age (range)** intervention group: 28.4 years (16-61 years) comparator group: 27.4 years (16-59 years) • **Body Mass Index (SD)** intervention group: 26.6 (4.4) comparator group: 26.2 (3.4) • **Diabetes** (%) intervention group: 2% comparator group: 0%
Interventions	• **Gentamicin collagen sponge** The cavity resulting from excision was packed with a collagen sponge containing gentamicin, before wound closure. The wound was closed in one layer with an interrupted monofilament non-absorbable suture in the midline. Subcutaneous sutures were not used and no systemic prophylactic antibiotic treatment was given.
Comparator	• **No antibiotics** No gentamicin collagen sponge was implanted. The wound was closed in one layer with an interrupted monofilament non-absorbable suture in the midline. Subcutaneous sutures were not used and no systemic prophylactic antibiotic treatment was given.
Outcome measure(s)	• **SSI** Authors defined SSI as non-healing wound and/or presence of exudate. No further information was provided.
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias

	Andersson (2010)
	Blinding of outcome assessment • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Partially directly applicable Criteria used to classify SSI not explicitly specified.

E.2 Bennett-Guerrero 2010a

Item	Bennett-Guerrero 2010 a
Title	Gentamicin-collagen sponge for infection prophylaxis in colorectal surgery
	Study type • Randomised controlled trial Multi-centre RCT. **Study details** • Study location US • **Study setting** Department of Surgery. • **Study dates** February 2008 and March 2009 • **Duration of follow-up** 60 days from surgery. • **Sources of funding** Supported by Innocoll Technologies.

Item	Bennett-Guerrero 2010 a
	Inclusion criteria • Patients 18 years or older and having 1 of 13 types of colorectal surgery scheduled. • Laparoscopically assisted procedures requiring an incision of at least 7 cm. **Exclusion criteria** • Presence of a clinically significant concomitant surgical procedure. • Use of a laparoscopic or other minimally invasive surgical procedure involving a laparotomy incision shorter than 7 cm. • Laparotomy within the 60 day period before the screening visit or a planned second laparotomy within the 60 day period after surgery • Situation in which it was technically impossible to insert two sponges above the fascia. • **Sample size** 602 **Sample characteristics** • **Split between study groups** Intervention group: 300 Comparator group: 302 • **Loss to follow-up** Intervention group: 3 Comparator group: 5 • **%female** Intervention group: 39.7% Comparator group: 47.7% • **Median Age (IQR)** Intervention group: 57.8 (45.5-67.7) Comparator group: 58.0 (47.4-67.0) • **Median Body Mass Index (range)** Intervention group: 26.8 (23.8-30.8) Comparator group: 27.2(24.0-30.8) • **Diabetes (%)** Intervention group: 12.3% Comparator group: 15.6%
Interventions	• **Gentamicin collagen sponge** Each sponge (10 by 10 cm) contained 280 mg of collagen and 130mg of gentamicin. In patients who were randomly assigned to receive a sponge, two sponges were inserted anteriorly to the fascia, along the full length of the incision, immediately before closure of

Item	Bennett-Guerrero 2010 a
	the surgical wound. Patients in which sponge group in whom re-exploration of the surgical site was necessary within 1 week after the first surgery had two new sponges inserted at the time of closure. Antibiotic prophylaxis was administered to patients.
Comparator	• **No antibiotics** No gentamicin collagen sponge was placed in the control group. Antibiotic prophylaxis was administered to patients.
Outcome measure(s)	• **SSI** Presence or absence, extent, and severity of all infections ascertained according to standardised criteria, including CDC criteria and Itani and colleagues. Possible wound infections were identified by events including signs of infection, administration of postoperative antibiotics, rehospitalisation, and death. • **Superficial SSI** Presence or absence, extent, and severity of all infections ascertained according to standardised criteria, including CDC criteria and Itani and colleagues. • **Deep SSI** Presence or absence, extent, and severity of all infections ascertained according to standardised criteria, including CDC criteria and Itani and colleagues. • **Organ/space SSI** Presence or absence, extent, and severity of all infections ascertained according to standardised criteria, including CDC criteria and Itani and colleagues. • **Length of hospital stay** • **Hospital readmission**
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • High risk of bias Surgeons were not blinded but patients and members of the adjudication committee were unware of allocation. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias

Item	Bennett-Guerrero 2010 a
	Selective reporting • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.3 Bennett-Guerrero 2010 b

Item	Bennett-Guerrero 2010b
Title	Effect of an implantable gentamicin-collagen sponge on sternal wound infections following cardiac surgery: a randomized trial
Study details	**Study type** • Randomised controlled trial Multi-centre RCT • **Study location** US • **Study setting** Not specified. • **Study dates** 21st December 2007 to 11th March 2009 • **Duration of follow-up** 90 days from surgery. • **Sources of funding** Study was sponsored by Innocoll Technologies Ltd. **Inclusion criteria** • Males and females ages 18 years or older • Scheduled to undergo non-emergent coronary bypass graft and/ or valve repair or replacement surgery through a full median sternotomy • At high risk of sternal wound infection, defined as the presence of diabetes mellitus, and/or obesity, defined as body mass index greater than 30.

Item	Bennett-Guerrero 2010b
	Exclusion criteria • History of hypersensitivity to gentamicin or bovine collagen • Emergency surgery • Significant concomitant surgical procedure • Minimally invasive or thoracic surgical approach • Pregnancy • Preoperative mechanical assist device or intraaortic balloon pump if inserted for shock or low output syndrome • Active and significant systemic infection • antibiotic therapy within 2 weeks preoperatively • preoperative serum creatinine level greater than 3 mg/dL • Malignancy except for squamous or basal cell carcinoma of the skin • Major organ transplantation • Significant drug or alcohol abuse • Receiving systemic immunosuppressive drugs, including steroids • scheduled to receive stress doses of glucocorticoids • Postsurgical life expectancy of 90 days or less • Participation in another experimental drug or device study • Refusal to accept medically indicated blood products. • **Sample size** 1502 **Sample characteristics** • **Split between study groups** Intervention group: 753 Comparator group: 749 • **Loss to follow-up** Intervention group: 13 Comparator group: 18 • **%female**

Item	Bennett-Guerrero 2010b
	Intervention group: 29.6% Comparator group: 29.2% • **Median Age (IQR)** Intervention group: 64.2 (58.0-71.5) Comparator group: 64.9 (57.2-72.1) • **Median Body Mass Index (range)** Intervention group: 33.1 (30.2-37.2) Comparator group: 32.8 (30.0-36.2) • **Diabetes (%)** Intervention group: 65.5% Comparator group: 68.5%
Interventions	• **Gentamicin collagen sponge** Each 100 cm2 (5x20 cm) sponge contained 280mg of collagen and 130 mg of gentamicin. Study participants received 2 sponges inserted between the sternal halves along the full length of the sternum immediately before closure of the sternum. The protocol called for patients randomised to the gentamicin- collagen sponge group and requiring re-exploration (e.g. due to bleeding) within 1 week after surgery to receive 2 new sponges inserted at the time of closure of the reoperation. Preoperatively, the use of nasal mupirocin prophylaxis was allowed but not required. Antibiotic prophylaxis was administered to patients.
Comparator	• **No antibiotics** The control group did not receive gentamicin collagen sponges. Preoperatively, the use of nasal mupirocin prophylaxis was allowed but not required. Antibiotic prophylaxis was administered to patients.
Outcome measure(s)	• **SSI** The presence or absence, extent and severity of all possible infections were classified using standardised criteria including those from CDC. Possible infections were identified by triggered events in the electronic case report form, including signs or symptoms of possible infection, administration of postoperative antibiotics, rehospitalisation, and death. • **Superficial SSI** The presence or absence, extent and severity of all possible infections were classified using standardised criteria including those from CDC. • **Deep SSI** The presence or absence, extent and severity of all possible infections were classified using standardised criteria including those from CDC. • **Length of hospital stay** • **Hospital readmission**

Item	Bennett-Guerrero 2010b
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias The randomisation scheme was stratified by site and random block sizes were used. However unclear how sequence was generated. **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • High risk of bias Surgeons were not blinded but patients and members of the adjudication committee were unware of allocation. However, study was not downgraded in this domain. **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.4 Buimer 2008

Item	Buimer (2008)
Title	Surgical treatment of hidradenitis suppurativa with gentamicin sulfate: a prospective randomized study
	Study type • Randomised controlled trial • **Study location** The Netherlands • **Study setting**

Item	Buimer (2008)
	Medical Centre • **Study dates** Not reported. • **Duration of follow-up** 1 week • **Sources of funding** Not specified. **Inclusion criteria** • Patients diagnosed with Hidradenitis Suppurativa. **Exclusion criteria** • None reported • **Sample size** 200 **Sample characteristics** • **Split between study groups** Intervention group: 124 Comparator group: 76 • **Loss to follow-up** Not reported. • **%female** Intervention group: 87% Comparator group: 95% • **Mean age (SD)** Intervention group: 31 (9) Comparator group: 31 (8)
Interventions	• **Gentamicin collagen sponge** In the intervention group, the hidradenitis suppurativa were excised with primary closure of the wound over a 5x5 cm gentamicin collagen sponge. The sponge contains 50 mg of gentamicin sulfate, comparable with 32.5 mg of gentamicin.
Comparator	• **No antibiotics**

Item	Buimer (2008)
	Hidradenitis suppurativa lesions were excised with primary closure of the wound without enclosure of antibiotics.
Outcome measure(s)	• **SSI** No classification criteria reported.
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias All patients assessed by same investigator. Unclear if the investigator was blinded. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate Unclear random sequence generation, allocation concealment and blinding of outcome assessment **Directness** • Partially directly applicable Criteria used for classification of surgical site infection not specified.

E.5 Collin 2013

Item	Collin (2013)
Title	Effect of local gentamicin-collagen on perineal wound complications and cancer recurrence after abdominoperineal resection: a multicentre randomized controlled trial.
	Study type • Randomised controlled trial • **Study location** Sweden • **Study setting** University hospital • **Study dates** February 2000 to April 2003 • **Duration of follow-up** 1 week, 1, 3 and 12 months. • **Sources of funding** Not specified. **Inclusion criteria** • Patients who underwent excision of the rectum for cancer or inflammatory bowel disease. **Exclusion criteria** • None reported • **Sample size** 102 **Sample characteristics** • **Split between study groups** Intervention group: 52 Comparator group: 50 • **Loss to follow-up** Not specified

Item	Collin (2013)
	• **%female** Intervention group: 38% Comparator group: 42% • **Median age (range)** Intervention group: 65 (29-87) Comparator group: 66.5 (35-85)
Interventions	• **Gentamicin collagen sponge** In patients randomised to treatment group, a 10x10cm gentamicin sponge was placed immediately distal to the levator ani muscle (if present) or in the anal canal if an intersphincteric excision had been performed. The perineal fat and skin were sutured in layers. If perineal drain was used, this was not placed in contact with the gentamicin-collagen sponge and was separated from the sponge by sutures. The gentamicin sponge was impregnated with 2.0 mg/cm2 of gentamicin sulfate. All patients has preoperative bowel preparation and antibiotic prophylaxis according to the local routines at each centre.
Comparator	• **No antibiotics** Patients underwent surgery alone (no sponge implanted). All patients has preoperative bowel preparation and antibiotic prophylaxis according to the local routines at each centre.
Outcome measure(s)	• **SSI** Perineal wounds classified as infected if following were present: - redness, swelling -purulent discharge - open infected wound.
New column	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • High risk of bias Patients and surgeons not blinded to randomisation. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • High risk of bias Surgeons performed follow-up not blinded. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias

Item	Collin (2013)
	Other sources of bias • Low risk of bias **Overall risk of bias** • Moderate *No blinding of outcome assessment.* **Directness** • Directly applicable

E.6 Cordtz 1989

Item	Cordtz (1989)
Title	The effect of incisional plastic drapes and redisinfection of operation site on wound infection following caesarean section
	Study type • Randomised controlled trial • **Study location** Denmark • **Study setting** Hospital setting • **Study dates** Not reported. • **Duration of follow-up** 2 weeks • **Sources of funding** Not reported **Inclusion criteria** • Women undergoing caesarean section. **Exclusion criteria** • Patients with history of iodine sensitivity.

Item	Cordtz (1989)
	• **Sample size** 1340 **Sample characteristics** • **Split between study groups** *Overall (includes patients who received drapes and no drapes)* Intervention group: 649 Comparator group: 691 *Drapes* Intervention group: 325 Comparator group: 337 *No drapes* Intervention group: 324 Comparator group: 354 • **Loss to follow-up** Not reported
Interventions	• **2.5% Iodine in 70% ethanol** For pre-operative skin disinfection 2.5% iodine in 70% ethanol was used. The patients were randomised to receive re-disinfection. Re-disinfection was defined as the disinfection of the skin around the incision, with 2.5% iodine in 70% alcohol, shortly before skin closure. Antibiotic prophylaxis, starting on the day of operation and discontinued after 2-4 days.
Comparator	• **No antiseptics** For pre-operative skin disinfection 2.5% iodine in 70% ethanol was used. The patients were randomised to receive no re-disinfection. Antibiotic prophylaxis, starting on the day of operation and discontinued after 2-4 days.
Outcome measure(s)	• **SSI** Wound infection recorded as: Possibly infected: localised erythema and/or serous secretion without presence of blood Infected: presence of pus irrespective of the results of bacteriological examination. Pus could be classified superficially or subfascially located.
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Unclear risk of bias Insufficient information provided.

Item	Cordtz (1989)
	Blinding of participants and personnel • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias Insufficient information provided. **Overall risk of bias** • Moderate Unclear random sequence generation, allocation concealment and blinding of outcome assessment. **Directness** • Directly applicable

E.7 Eklund 2005

Item	Eklund (2005)
Title	Prophylaxis of sternal wound infections with gentamicin-collagen implant: randomized controlled study in cardiac surgery
	Study type • Randomised controlled trial • **Study location** Finland • **Study setting** University hospital • **Study dates** July 1998 and September 1999 • **Duration of follow-up** 3 months

Item	Eklund (2005)
	• **Sources of funding** The study was supported by grants from Helsinki University Central Hospital and Schering Plough Corporation. **Inclusion criteria** • Patients who underwent elective CABG surgery. **Exclusion criteria** • Allergy to gentamicin or to multiple drugs • had severe renal insufficiency (uraemia or need for dialysis) • had previous kidney transplant or a redo procedure • Non-nationals. • **Sample size** 542 **Sample characteristics** • **Split between study groups** Intervention group: 272 Comparator group: 270 • **Loss to follow-up** Not reported • **%female** Intervention group: 24% Comparator group: 29% • **Mean age (SD)** Intervention group: 64.4 (9.3) Comparator group: 64.7 (9.3) • **Diabetes (%)** Intervention group: 22% Comparator group: 23% • **COPD (%)** Intervention group: 9% Comparator group: 10%
Interventions	• **Gentamicin collagen sponge**

Item	Eklund (2005)
	The patients in the gentamicin group received a 10cmx 10cm gentamicin- collagen implant which contains 13 mg gentamicin and 280mg collagen, underneath their sternum before wound closure. All patients received antibiotic prophylaxis with two doses of intravenous cefuroxime 1.5g in 6h. The patients that were hospitalised at least three days pre-operatively also received vancomycin 500 mg on two occasions.
Comparator	• **No antibiotics** The controls' sternums were closed in a routine manner with steel wires, without gentamicin implants. All patients received antibiotic prophylaxis with two doses of intravenous cefuroxime 1.5g in 6h. The patients that were hospitalised at least three days pre-operatively also received vancomycin 500 mg on two occasions.
Outcome measure(s)	• **SSI** Assessment of SSIs was made according to the CDC criteria. • **Superficial SSI** Assessment of SSIs was made according to the CDC criteria. • **Deep SSI** Assessment of SSIs was made according to the CDC criteria. • **Organ/space SSI** Assessment of SSIs was made according to the CDC criteria. The diagnosis of mediastinitis was based on clinical signs, the results of wound and blood cultures and computed tomography, positive culture from mediastinal tissue, or clinical evidence of mediastinitis in surgery. The diagnosis of sternum infection was made either by a cardiac surgeon or an infection consultant. • **Mortality post-surgery**
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Unclear risk of bias Unclear if patients were blinded. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting**

Item	Eklund (2005)
	• Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.8 Evans 1974

Item	Evans (1974)
Title	The reduction of surgical wound infections by topical cephaloridine: a controlled clinical trial
	Study type • Randomised controlled trial • **Study location** UK • **Study setting** Hospital setting. • **Study dates** Not specified. • **Duration of follow-up** 4 weeks. • **Sources of funding** Glaxo Laboratories Ltd provided the cephaloridine (Ceporin). **Inclusion criteria** • All operation cases involving a sutured incision more than 3 cm long. **Exclusion criteria** • Perineal wound of an abdominal perineal excision of the rectum. **Sample size** • 406 **Sample characteristics**

Item	Evans (1974)
	• **Split between study groups** Intervention group: 188 Comparator group: 213 • **Loss to follow-up** 5 patients died within 4 weeks of operation.
Interventions	• **Cephaloridine** 1g of cephaloridine in 2ml of water was instilled into the wound before closure. The volume of solution was limited to 2ml as the purpose was to leave the whole dose in the wound rather than to irrigate with a large volume and waste most of the antibiotic. No restrictions were placed on antibiotic therapy when clinically indicated.
Comparator	• **No antibiotics** No antibiotics were used before wound closure. No restrictions were placed on antibiotic therapy when clinically indicated.
Outcome measure(s)	• **SSI** Wound infection was defined as the discharge of pus from the wound. This was usually a small amount (e.g. a stitch abscess) but sometimes a wound abscess developed which required evacuation, and some infections followed the discharge of wound haematomas. When the wound discharged pus in hospital a swab was taken for culture.
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias Baseline patient characteristics not reported to evaluate baseline imbalances.

Item	Evans (1974)
	Overall risk of bias • Moderate Unclear allocation concealment and other sources of bias. **Directness** • Directly applicable

E.9 Friberg 2005

Item	Friberg (2005) Secondary publication: Frigberg (2007)
Title	Local gentamicin reduces sternal wound infections after cardiac surgery: a randomized controlled trial Local collagen-gentamicin for prevention of sternal wound infections: the LOGIP trial
New column	**Study type** • Randomised controlled trial • **Study location** Sweden • **Study setting** Cardiothoracic centres • **Study dates** September 2000 to September 2002 • **Duration of follow-up** 2 months postoperatively • **Sources of funding** Study financed by grants from the Research Committee of Orebro County Council and from Schering-Plough, who also provided free Collamtamp-G. **Inclusion criteria** • All patients undergoing cardiac surgery through median sternotomy including operations on the ascending aorta. **Exclusion criteria** • Known allergy to gentamicin • Pregnancy or breastfeeding • treatment with aminoglucosides during the last 2 weeks before surgery • expected difficulty in fulfilling the follow-up requirements, for linguistic or other reasons.

Item	Friberg (2005) Secondary publication: Frigberg (2007)
	• **Sample size** 1950 **Sample characteristics** • **Split between study groups** Intervention group: 1000 Comparator group: 1000 • **Loss to follow-up** Intervention group:12 (11 declined further participation and 1 could not be reached) Comparator group: 29 (24 declined further participation and 5 could not be reached) • **%female** Intervention group: 24% Comparator group: 23.4% • **Median age (range)** Intervention group: 68 (20-87) Comparator group: 68 (25-87) • **Median Body Mass Index (range)** Intervention group: 26.6 (14.8-46.1) Comparator group: 26.3 (15.6-42.8) • **Diabetes (%)** Intervention group: 18% Comparator group: 18.3% • **COPD (%)** Intervention group: 6% Comparator group: 5.3%
Interventions	• **Gentamicin collagen sponge** Collatamp-G consists of a flat absorbable bovine collagen sponge with gentamicin sulfate. A 10x10x0.5 cm sponge contains 280 mg collagen and 130mg gentamicin. The treatment group received two such sponges in the wound immediately before closure. The sponges were cut into appropriate sizes and put between the sternal halves. More than two layers of Collatamp-G were avoided so as not to compromise sternal healing and stability, and any leftover sponge was put behind the sternum at the proximal or distal end. The group also received routine antibiotic prophylaxis.
Comparator	• **No antibiotics**

Item	Friberg (2005) Secondary publication: Frigberg (2007)
	In the control group the wound was closed in a conventional way. The control group received routine antibiotic prophylaxis.
Outcome measure(s)	• **SSI** Criteria for definition and classification of surgical site infection according to CDC were used with minor modification: Depth 1 (cutis) e.g. infected crusts and Depth 2 (subcutis) involving subcutaneous tissue but not reaching down to sternal fixation wires was considered as a superficial SSI. Depth 3 (presternal), infections reaching below the superficial fascia, involving sternal wires and Depth 4 (sternal bone or mediastinum), and unstable sternal fixation with signs of osteomyelitis or positive bacterial cultures from mediastinum or mediastinal abscess were considered as deep SSI. • **Superficial SSI** Depth 1 (cutis) e.g. infected crusts and Depth 2 (subcutis) involving subcutaneous tissue but not reaching down to sternal fixation wires was considered as a superficial SSI. • **Deep SSI** Depth 3 (presternal), infections reaching below the superficial fascia, involving sternal wires and Depth 4 (sternal bone or mediastinum), and unstable sternal fixation with signs of osteomyelitis or positive bacterial cultures from mediastinum or mediastinal abscess were considered as deep SSI. • **Mortality post-surgery** Hospital mortality and total 60 day mortality
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias**

Item	Friberg (2005) Secondary publication: Frigberg (2007)
	• Low **Directness** • Directly applicable

E.10 Gray 1981

Item	Gray (1981)
Title	The effect of topical povidone iodine on wound infection following abdominal surgery
	Study type • Randomised controlled trial • **Study location** UK • **Study setting** Surgical Department • **Study dates** Not specified • **Duration of follow-up** 2 weeks • **Sources of funding** Not specified. **Inclusion criteria** • All patients undergoing elective abdominal surgery under the care of one consultant surgeon. • Emergency cases not entered as it was felt that it would be difficult to maintain strict adherence to the protocol. **Exclusion criteria** • Known allergy to iodine. • **Sample size** 156

Item	Gray (1981)
	Sample characteristics • **Split between study groups** Intervention group: 71 Comparator group: 82 • **Loss to follow-up** 3 patients excluded from analysis as they died within 2 weeks of operation. • **%female** Intervention group: 54% Comparator group: 56% • **Mean Age (range)** Intervention group Males: 56 (27-76) Females: 61 (25-82) Comparator group Males: 55 (16-76) Females: 59 (22-83)
Interventions	• **Povidone Iodine** The patients in the treatment group were sprayed with Disadine DP, a dry powder povidone iodine spray delivering 0.5% available iodine. Spraying was performed from a distance of about 25 cm until the whole of the wound had received a light dusting of powder.
Comparator	• **No antiseptics**
Outcome measure(s)	• **SSI** The wounds were classified as: A. major infection with copious purulent discharge B. minor infection with scanty discharge of pus C. non-infected • **Postoperative antibiotic use**
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Unclear risk of bias Unclear if house surgeon was blinded.. **Incomplete outcome data**

Item	Gray (1981)
	• Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.11 Gruessner 2001

Item	Gruessner (2001)
Title	Improvement of perineal wound healing by local administration of gentamicin-impregnated collagen fleeces after abdominoperineal excision of rectal cancer.
	Study type • Randomised controlled trial • **Study location** Germany • **Study setting** Not specified. • **Study dates** Not specified. • **Duration of follow-up** 8 weeks • **Sources of funding** Not specified. **Inclusion criteria** • Aged 18 years and older •Patients with abdominoperineal resection (APR) for low rectal carcinoma (<8 cm, measured from the dentate line) that could not be treated by sphincter-saving radical resection • sacral wound cavity, into which 3 gentamicin- collagen fleeces would be inserted without surgical or technical difficulties.

Item	Gruessner (2001)
	Exclusion criteria • Antibiotic treatment within 2days prior to surgery • Preoperative orthograde intestinal lavage within an antibiotic solution. • Blood donation (including plasmapheresis) of 500 mL within 3 months prior to treatment (with the exception of preoperative autologous blood donation) • excess weight (more than 35% above normal) • Concomitant immunosuppressive therapy or steroid therapy • Rectum perforations or emergency interventions. • **Sample size** 97 **Sample characteristics** • **Split between study groups** Intervention group: 49 Comparator group: 48 • **Loss to follow-up** Not reported. • **Median age (range)** Intervention group: 61.9 (44-83) Comparator group: 63.2 (41-90) • **Diabetes (%)** Intervention group: 8% Comparator group: 14%
Interventions	• **Gentamicin collagen sponge** Group received closure of the pelvic floor, mandatory insertion of a sacral overflow drain, and multiple-layer primary wound management. This group additionally received three gentamicin fleeces that were evenly inserted into the sacral wound cavity at one level with the remnants of the M. levator ani. Preoperatively all patients received orthograde intestinal lavages standard preparation as well as a single antibiotic dose of 2g of cefazolin and 500 mg of metronidazole at the time of skin incision.
Comparator	• **No antibiotics** Control group received complete closure of the pelvic floor, mandatory insertion of a sacral overflow drain, and multiple-layer primary wound management. Preoperatively all patients received orthograde intestinal lavages standard preparation as well as a single antibiotic dose of 2g of cefazolin and 500 mg of metronidazole at the time of skin incision.
Outcome measure(s)	• **SSI** Criteria used for classification not specified. Study states that the quantity of wound secretion obtained by means of drainage was documented and analysed with respect to its gentamicin concentration and bacteriologic contamination.

Item	Gruessner (2001)
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias Insufficient information provided. **Overall risk of bias** • Moderate Unclear random sequence generation, allocation concealment and blinding of outcome assessment. **Directness** • Partially directly applicable Criteria used for classification of surgical site infection not specified.

E.12 Haase 2005

Item	Haase (2005)
Title	Subcutaneous gentamycin implant to reduce wound infections after loop-ileostomy closure: a randomized, double-blind, placebo-controlled trial

Item	Haase (2005)
	Study type • Randomised controlled trial • **Study location** Germany • **Study setting** Department of General, visceral and thoracic surgery • **Study dates** May 2000 to June 2003 • **Duration of follow-up** within 30 days • **Sources of funding** Not specified. **Inclusion criteria** • Patients admitted for closure of a loop ileostomy. **Exclusion criteria** • Refusal to participate • Patients with known immunologic disease or immunosuppressive therapy • Known allergic reaction to gentamicin or animal collagen • simultaneous abdominal operation • history of chronic alcohol or drug abuse • renal insufficiency. • **Sample size** 82 **Sample characteristics** • **Split between study groups** Intervention group: 40 Comparator group: 42 • **Loss to follow-up** Not reported • **%female** Intervention group: 40%

Item	Haase (2005)
	Comparator group: 38% • **Mean age (SD)** Intervention group: 65.8 (11.5) Comparator group: 64.8 (9.9) • **Diabetes (%)** Intervention group: 15% Comparator group: 12%
Interventions	• **Gentamicin collagen sponge** The gentamicin implant was placed subcutaneously. On the day before surgery all patients underwent a standard bowel preparation. Patients' received cefuroxime and metronidazole. Systemic antibiotic therapy was not routinely given postoperatively..
Comparator	• **Placebo** The collagen implant was placed subcutaneously. On the day before surgery all patients underwent a standard bowel preparation. Patients received cefuroxime and metronidazole. Systemic antibiotic therapy was not routinely given postoperatively.
Outcome measure(s)	• **SSI** Wound infection was defined according to the CDC. An infection was documented it if occurred within 30 days of the operation and involved only skin or subcutaneous tissue (superficial infection) or deep soft tissue e.g. fascial or muscle layers (deep infection). Patients with wound infection had to satisfy at least one of the following criteria: 1. purulent wound drainage 2. Isolated microbes taken in a swab from the wound 3. At least one of the following signs: pain, tenderness, swelling, redness, or heat. • **Superficial SSI** Wound infection was defined according to the CDC. An infection was documented it if occurred within 30 days of the operation and involved only skin or subcutaneous tissue (superficial infection) or deep soft tissue e.g. fascial or muscle layers (deep infection). Patients with wound infection had to satisfy at least one of the following criteria: 1. purulent wound drainage 2. Isolated microbes taken in a swab from the wound 3. At least one of the following signs: pain, tenderness, swelling, redness, or heat. • **Deep SSI** Wound infection was defined according to the CDC. An infection was documented it if occurred within 30 days of the operation and involved only skin or subcutaneous tissue (superficial infection) or deep soft tissue e.g. fascial or muscle layers (deep infection). Patients with wound infection had to satisfy at least one of the following criteria: 1. purulent wound drainage 2. isolated microbes taken in a a swab from the wound 3. At least one of the following signs: pain, tenderness, swelling, redness, or heat.
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel**

Item	Haase (2005)
	• Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.13 Harihara 2006

Item	Harihara (2006)
Title	Effects of applying povidone-iodine just before skin closure
	Study type • Randomised controlled trial • **Study location** Japan • **Study setting** Department of surgery. • **Study dates** July 2004 and December 2004 • **Duration of follow-up** Not specified. • **Sources of funding** No specified. **Inclusion criteria**

Item	Harihara (2006)
	• Patients undergoing gastric and colorectal surgery. **Exclusion criteria** • None reported • **Sample size** 107 cases of gastric surgery and colorectal surgery. **Sample characteristics** • **Split between study groups** Intervention group: 54 Comparator group: 53 • **Loss to follow-up** Not reported. • **%female** *Gastric surgery* Intervention group: 78% Comparator group: 83% *Colorectal surgery* Intervention group: 54% Comparator group: 53% • **Mean age (SD)** *Gastric surgery* Intervention group:62.1 (11.9) Comparator group: 65.0 (11.9) *Colorectal surgery* Intervention group:62.8 (12.3) Comparator group:66.3 (11.5) • **Body Mass Index (SD)** *Colorectal surgery* Intervention group: 23.1 (3.4) Comparator group: 21.8 (3.2) • **Diabetes (%)** Colorectal surgery

Item	Harihara (2006)
	Intervention group: 10% Comparator group: 16%
Interventions	• **Povidone Iodine** Povidone iodine was applied to the skin around the incision skin preparation after subcutaneous irrigation and before skin closure. Skin was prepared in the same manner as the preoperative skin preparation.
Comparator	• **No antiseptics** No antiseptic was used before skin closure.
Outcome measure(s)	• **SSI** Criteria used for defining SSI were according to the JNIS system that is a Japanese modification of the CDC NNIS system.
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate Unclear random sequence generation, allocation concealment and blinding of outcome assessment. **Directness**

Item	Harihara (2006)
	• Partially directly applicable Follow-up period not specified.

E.14 Hinarejos 2013

Item	Hinarejos (2013)
Title	The use of erythromycin and colistin-loaded cement in total knee arthroplasty does not reduce the incidence of infection: a prospective randomized study in 3000 knees
	Study type • Randomised controlled trial • **Study location** Spain • **Study setting** Departments of Orthopaedic Surgery and Infectious Diseases. • **Study dates** September 2005 to April 2010. • **Duration of follow-up** 12 months. • **Sources of funding** Not specified. **Inclusion criteria** • Patients with any diagnosis leading to total knee arthroplasty. **Exclusion criteria** • History of infection in the knee • History of allergy to one or both of the antibiotics used in the cement. • **Sample size** 3000 knees **Sample characteristics**

Item	Hinarejos (2013)
	• **Split between study groups** Intervention group: 1483 Comparator group: 1465 • **Loss to follow-up** 52 knees were lost before one year of follow-up. • **%female** Intervention group: 76.7% Comparator group: 75.9% • **Mean age (SD)** Intervention group: 75.84 (7.44) Comparator group: 76.06 (7.22) • **Body Mass Index (SD)** Intervention group: 31.50 (5.09) Comparator group: 31.74 (5.07) • **Diabetes (%)** Intervention group: 16.5% Comparator group: 17.7%
Interventions	• **Erythromycin and colistin-loaded cement** Simplex P cement leaded with 0.5g of erythromycin and three million units of colistin in 40g of cement (Stryker) The cement was mechanically mixed under vacuum conditions. In all patients, preoperative intravenous prophylactic antibiotics were administered.
Comparator	• **No antibiotics** Prosthesis was cemented with Simplex cement without antibiotic. Cement was mechanically mixed under vacuum conditions. In all patients, preoperative intravenous prophylactic antibiotics were administered.
Outcome measure(s)	• **SSI** The diagnosis of infection and its classification was made according to the criteria of the Centres for Disease Control and Prevention by the surgeon in 95% of the forty knees. • **Superficial SSI** The diagnosis of infection and its classification was made according to the criteria of the Centres for Disease Control and Prevention by the surgeon in 95% of the forty knees. • **Deep SSI** The diagnosis of infection and its classification was made according to the criteria of the Centres for Disease Control and Prevention by the surgeon in 95% of the forty knees.
Risk of bias	**Random sequence generation**

Item	Hinarejos (2013)
Directness	• Low risk of bias **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • High risk of bias Open label study. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate Unclear allocation concealment and blinding of outcome assessment. **Directness** • Directly applicable

E.15 Migaczewski 2012

Item	Migaczewski (2012)
Title	Prevention of early infective complications after laparoscopic splenectomy with the Garamycin sponge
	Study type • Randomised controlled trial • **Study location** Poland • **Study setting** not specified

Item	Migaczewski (2012)
	• **Study dates** September 2007 to December 2009 • **Duration of follow-up** 1 month (30 days) • **Sources of funding** not reported **Inclusion criteria** • Patients with idiopathic thrombocytopenic purpura (ITP) or non-Hodgkin lymphoma (NHL) who were undergoing laparoscopic splenectomy were included. **Exclusion criteria** • patients with idiopathic thrombocytopenic purpura treated by non-steroidal methods (such as, immunoglobulins or immunosuppression) • extreme thrombocytopenia • presented with active bacterial infection • history of other diseases influencing bacterial resistance • diagnosis of splenomegaly and/or hypersplenism • required conversion to an open surgery • intraoperative iatrogenic gastric perforation • **Sample size** n = 60 participants: 40 with ITP and 20 with NHL **Sample characteristics** • **Split between study groups** intervention group, 20 with ITP and 10 with NHL; comparator group 20 with ITP and 10 with NHL • **Loss to follow-up** no losses to follow-up were reported • **%female** intervention group - ITP patients, 65%; NHL patients, 40% comparator group - ITP patients, 70%; NHL patients, 40% • **Mean age (SD)** intervention group - ITP patients, 41.6 years (19.8); NHL patients, 56.4 years (7.1) comparator group - ITP patients, 39.2 years (14.2); NHL patients, 55.3 years (15.2)

Item	Migaczewski (2012)
Interventions	• **Gentamicin collagen sponge** All participants' received a pneumococcal vaccine and antibiotic prophylaxis using ceftriaxone. Following laparoscopic splenectomy, a gentamicin collagen sponge was left at the splenic site. Closed gravity 16 F drains were employed at the splenic site. They were left until the amount of drained fluid was less than 50 cm3 per day. In all the patients' routine prophylaxis of infective complications after splenectomy was carried out.
Comparator	• **No antibiotics** All participants' received a pneumococcal vaccine and antibiotic prophylaxis using ceftriaxone. Following laparoscopic splenectomy, no sponge was left at the splenic site. Closed gravity 16 F drains were employed at the splenic site. They were left until the amount of drained fluid was less than 50 cm3 per day. In all the patients' routine prophylaxis of infective complications after splenectomy was carried out.
Outcome measure(s)	• **SSI** No definitions or criteria for categorising SSI were reported
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate

Item	Migaczewski (2012)
	Unclear random sequence generation, allocation concealment and blinding of outcome assessment. **Directness** • Partially directly applicable No definitions or criteria for categorising SSI were reported.

E.16 Moesgaard 1989

Item	Moesgaard (1989)
Title	Intraincisional antibiotic in addition to systemic antibiotic treatment fails to reduce wound infection rates in contaminated abdominal surgery. A controlled clinical trial
	Study type • Randomised controlled trial • **Study location** Denmark • **Study setting** Department of surgical gastroenterology • **Study dates** April 1983 to January 1986 • **Duration of follow-up** One month • **Sources of funding** Not specified **Inclusion criteria** • All patients evaluated for study in three participating hospitals if generalised or localised peritonitis (including intraperitoneal abscess) was present at the time of intra-abdominal operation. **Exclusion criteria** •Known hypersensitivity to cephalosporins or metronidazole •Antimicrobial drug administration within 4 days before surgery • Pregnancy • Verified immunologic defects • children below the age of 13 years.

Item	Moesgaard (1989)
	• **Sample size** 178 **Sample characteristics** • **Split between study groups** Intervention group: 91 Comparator group: 87 • **Loss to follow-up** Not reported. • **%female** Intervention group: 52% Comparator group: 53% • **Median age (range)** Intervention group: 58 (13-95) Comparator group: 56 (13-92)
Interventions	• **Cefotaxime** In patients allocated to intra-incisional antibiotic prophylaxis, cefotaxime 2mg, was applied topically to the subcutaneous layer at the time of wound closure. All patients received cefotaxime 2mg intravenously and metronidazole, 500 mg intravenously, preoperatively or intraoperatively, and the same doses every 8 hours for the next 72 hours.
Comparator	• **No antibiotics** No antibiotics were used before skin closure. All patients received cefotaxime 2mg intravenously and metronidazole, 500 mg intravenously, preoperatively or intraoperatively, and the same doses every 8 hours for the next 72 hours.
Outcome measure(s)	• **SSI** Wound infection was defined as accumulation of pus, draining spontaneously or after opening the wound. • **Organ/space SSI** Diagnosis of intraabdominal abscess was accepted only if proven by surgical drainage or by ultrasound-guided aspiration. • **Infectious complication: septicaemia** Diagnosis of septicaemia required positive blood culture.
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Unclear risk of bias

Item	Moesgaard (1989)
	Blinding of participants and personnel • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate Unclear random sequence generation and allocation concealment. **Directness** • Directly applicable

E.17 Musella 2001

Item	Musella (2001)
Title	Collagen tampons as aminoglycoside carriers to reduce postoperative infection rate in prosthetic repair of groin hernias.
	Study type • Randomised controlled trial • **Study location** Italy • **Study setting** University Hospital • **Study dates** January 1991 to January 1999 • **Duration of follow-up** 6 months • **Sources of funding** Not specified.

Item	Musella (2001)
	Inclusion criteria • Patients undergoing groin hernia repair. **Exclusion criteria** • Patients operated on as emergencies • Patients with diabetes, cancer, systemic infections or an abdominal aortic aneurysm • Patients having immunosuppressive treatment. • **Sample size** 595 **Sample characteristics** • **Split between study groups** Intervention group: 293 Comparator group: 284 • **Loss to follow-up** 18 patients were lost to follow up. • **%female** Intervention group: 5.1% Comparator group: 4.9% • **Mean Age** Intervention group: 53.2 Comparator group: 51.4
Interventions	• **Gentamicin collagen sponge** Absorbable collagen tampon (Collatamp G Innocol, Saal/Donau, Germany) treated with gentamicin, was placed in from to the prosthetic mesh, tailored to the patient and covered by sutured aponeurosis of the external oblique muscle. Patients were given long acting cephalosporin, ceftriaxone 2g systemically, 1 hour before and 12 hours after the intervention, at home if discharged from hospital.
Comparator	• **No antibiotics** Patients in the control group had a standard surgical treatment. Patients were given long acting cephalosporin, ceftriaxone 2g systemically, 1 hour before and 12 hours after the intervention, at home if discharged from hospital.
Outcome measure(s)	• **SSI** Criteria used for classification not specified.
Risk of bias	**Random sequence generation**

Item	Musella (2001)
Directness	• Unclear risk of bias Insufficient information provided. **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. However, the study was not downgraded in this domain. **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate Unclear random sequence generation and allocation concealment. **Directness** • Partially directly applicable Criteria used for classification of surgical site infection not specified.

E.18 Nowacki 2005

Item	Nowacki (2005)
Title	Prospective, randomized trial examining the role of gentamycin-containing collagen sponge in the reduction of postoperative morbidity in rectal cancer patients: early results and surprising outcome at 3-year follow-up
	Study type • Randomised controlled trial

Item	Nowacki (2005)

	• **Study location**
	Poland
	• **Study setting**
	not specified
	• **Study dates**
	January 1997 to April 1999
	• **Duration of follow-up**
	1 month (30 days)
	• **Sources of funding**
	not reported
	
	Inclusion criteria
	• Patients undergoing surgical resection of rectal cancer were included. They qualified for inclusion when the following types of elective surgery was planned: anterior resection, low-anterior resection, abdomino-perineal resection or Hartmann procedure.
	
	Exclusion criteria
	• poor general condition (WHO performance score > 2)
	• receiving steroids
	• anaemia
	• protracted diabetes (of more than 10 years)
	
	• **Sample size**
	n = 229 participants
	
	Sample characteristics
	• **Split between study groups**
	intervention group = 113;
	comparator group =116
	• **Loss to follow-up**
	intervention group = 7;
	comparator group = 4
	• **%female**
	intervention group, 40.6%;
	comparator group, 45.5%
	• **Median age (range)**
	intervention group, 60 years (18-89) ;

Item	Nowacki (2005)
	comparator group, 63 years (25-89)
Interventions	• **Gentamicin collagen sponge** All participants' received antibiotic prophylaxis using metronidazole and cefuroxime, as well as anticoagulant therapy. Different types of resections were performed depending on the distance between the anal verge and the lower border of the tumour, sphincter function, and the stage of cancer disease. Following resection, a gentamicin collagen sponge (containing 130 mg gentamicin sulphate) was placed into the parasacral area, always below the periotoneal reflection. When anterior resection was performed, the sponge was wrapped around the anastomosis. Peritoneal cavity lavage and drainage of the pelvic cavity were routinely performed.
Comparator	• **No antibiotics** No sponge was used. All participants' received antibiotic prophylaxis using metronidazole and cefuroxime, as well as anticoagulant therapy. Different types of resections were performed depending on the distance between the anal verge and the lower border of the tumour, sphincter function, and the stage of cancer disease. Following resection, no collagen sponge was placed at the surgical sites. Peritoneal cavity lavage and drainage of the pelvic cavity were routinely performed.
Outcome measure(s)	• **SSI** no definitions or criteria for categorising SSI were reported
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias

Item	Nowacki (2005)
	Overall risk of bias • Moderate Unclear random sequence generation, allocation concealment and blinding of outcome assessment. **Directness** • Partially directly applicable No definitions or criteria for categorising SSI were reported.

E.19 Ozbalci 2014

Item	Ozbalci (2014)
Title	Is gentamicin-impregnated collagen sponge to be recommended in pilonidal sinus patient treated with marsupialization? A prospective randomized study
	Study type • Randomised controlled trial • **Study location** Turkey • **Study setting** Department of general Surgery • **Study dates** January 2011 and December 2012 • **Duration of follow-up** 6- 30 months • **Sources of funding** Not specified **Inclusion criteria** • Patients undergoing surgery for pilonidal sinus. **Exclusion criteria** •Patients with diabetes.

Item	Ozbalci (2014)
	• **Sample size** 50 **Sample characteristics** • **Split between study groups** Intervention group: 25 Comparator group: 25 • **Loss to follow-up** Not specified. • **%female** Intervention group: 12% Comparator group: 23% • **Mean age (SD)** Intervention group: 26.4 (6.19) Comparator group: 27.4 (6.05)
Interventions	• **Gentamicin collagen sponge** All patients were operated under spinal or general anaesthesia in prone position. Patients in the group received gentamicin impregnated collagen sponge prepared in accordance with the size of the wound and defect was covered. The patients did not receive topical or systemic antibiotic treatment.
Comparator	• **No antibiotics** All patients were operated under spinal or general anaesthesia in prone position. Patients in this group did not receive gentamicin sponge. The patients did not receive topical or systemic antibiotic treatment.
Outcome measure(s)	• **SSI** Classification criteria used not specified.
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** •Unclear risk of bias

Item	Ozbalci (2014)
	Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias Insufficient information provided. **Overall risk of bias** • Moderate Unclear random sequence generation, allocation concealment and blinding of outcome assessment. **Directness** • Partially directly applicable Criteria used for classification of surgical site infection not specified.

E.20 Parker 1985

Item	Parker (1985)
Title	Systemic metronidazole combined with either topical povidone-iodine or ampicillin in acute appendicitis
	Study type • Randomised controlled trial • **Study location** UK • **Study setting** Hospital setting • **Study dates** Not specified. • **Duration of follow-up**

Item	Parker (1985)
	1 month • **Sources of funding** Napp laboratories supplied materials for study. **Inclusion criteria** •Patients undergoing appendectomy either electively or for clinically diagnosed appendicitis. **Exclusion criteria** • None reported • **Sample size** 100 **Sample characteristics** • **Split between study groups** Intervention group: 50 Comparator group: 50 • **Loss to follow-up** Not specified. • **%female** 60% • **Age range** 7-74 years.
Interventions	• **Povidone Iodine** 2ml of topical povidone iodine spray (Betadine antiseptic spray). All patients also received metronidazole by suppository for 48 h commencing 1 h before operation at the standard recommended dose of 1g tds. In children under 10 years this was reduced to 1/2g tds.
Comparator	• **Different antibiotics** Ampicillin powder 1g of ampicillin powder applied topically into the wound at the time of closure.
Outcome measure(s)	• **SSI** The wound was graded clean or infected where infection was understood to mean the presence of pus. No further information provided.
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias

Item	Parker (1985)
	Insufficient information provided. **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • High risk of bias Interim wound infections were reported by patients and bacteriology of the infected wounds was not taken, since all patients were discharged from the hospital on day 3 and at the outpatient review 1 month postoperatively, all wounds that had been infected had either partially or completely resolved after spontaneous discharge of pus. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias Insufficient information provided. **Overall risk of bias** • High Unclear random sequence generation and allocation concealment. Interim outcomes were reported were reported by patients, unclear if patients were blinded. **Directness** • Partially directly applicable Criteria used to classify SSI not explicitly specified.

E.21 Pochhammer 2015

Item	Pochhammer (2015)
Title	Subcutaneous application of gentamicin collagen implants as prophylaxis of surgical site infections in laparoscopic colorectal surgery: a randomized, double-blinded, three-arm trial

	Study type
	• Randomised controlled trial
	
	• **Study location**
	Germany
	• **Study setting**
	Single centre
	• **Study dates**
	July 2008 to July 2010
	• **Duration of follow-up**
	1 month (30 days)
	• **Sources of funding**
	Authors reported that medical device manufacturers provided gentamicin-collagen and collagen-only sponges and no further funding was given.
	
	Inclusion criteria
	• All adult patients scheduled for elective laparoscopic colorectal surgery eligible for inclusion.
	
	Exclusion criteria
	• known allergy to gentamicin or animal collagen
	• expected incompliance
	• intraoperative conversion to open surgery
	
	• **Sample size**
	n = 290 participants
	
	Sample characteristics
	• **Split between study groups**
	intervention group = 98;
	collagen-alone group = 96;
	control group = 97
	• **Loss to follow-up**

Item	Pochhammer (2015)
	1 participant in the intervention group was lost-to-follow-up • **%female** intervention group, 58.8%; collagen-alone group, 59.3%; control group, 49.5% • **Mean age (SD)** intervention group, 64.3 years (12.9); collagen-alone group, 67.1 years (12.9); control group, 66.0 years (12.3) • **Body Mass Index (SD)** intervention group, 26.6 (4.2); collagen-alone group, 26.2 years (5.1); control group, 26.2 (4.3)
New column	• **Gentamicin collagen sponge** All participants received preoperative antibiotic prophylaxis using ampicillin, sulbactam, ceftriaxone, levofloxacin or metronidazole, depending on the type of surgery performed. A collagen sponge containing 12.5 mg gentamicin sulphate was inserted subcutaneously after closing the peritoneum and aponeurosis separately with a running polyglactin suture at the bowel extraction site. A subcutaneous drain was not allowed and surgeons were free to perform a subcutaneous suture.
Comparator	• **Placebo** All participants' received preoperative antibiotic prophylaxis using ampicillin, sulbactam, ceftriaxone, levofloxacin or metronidazole, depending on the type of surgery performed. A collagen sponge without any antibiotics was inserted subcutaneously after closing the peritoneum and aponeurosis separately with a running polyglactin suture at the bowel extraction site. A subcutaneous drain was not allowed and surgeons were free to perform a subcutaneous suture. • **No antibiotics** No antibiotics were used before skin closure. All participants' received preoperative antibiotic prophylaxis using ampicillin, sulbactam, ceftriaxone, levofloxacin or metronidazole, depending on the type of surgery performed. No sponge was placed at the surgical site.
Outcome measure(s)	• **Superficial SSI** as defined by the CDC • **Deep SSI** as defined by the CDC • **Length of hospital stay**
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment**

Item	Pochhammer (2015)
	• Low risk of bias **Blinding of participants and personnel** • Low risk of bias Patients were blinded to group allocations. However, surgical staff could not aware of the assignment to no sponge group (control) but not the collagen sponge group (placebo). *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.22 Rickett 1969

Item	Rickett (1969)
Title	Topical ampicillin in the appendectomy wound: report of double-blind trial
	Study type • Randomised controlled trial • **Study location** UK • **Study setting** Not specified. • **Study dates** May and September 1968.

Item	Rickett (1969)
	• **Duration of follow-up** 3 weeks after surgery. • **Sources of funding** Beecham Research Laboratories supplied specially packaged phials of ampicillin and placebo. **Inclusion criteria** • Patients undergoing appendectomy. These included not only operations for acute appendicitis but also cold appendectomies, on the grounds that there may be a significant incidence of wound infection in these non-inflamed cases. **Exclusion criteria** •Patients with history of penicillin sensitivity. **• Sample size** 133 **Sample characteristics** • **Split between study groups** Intervention group: 64 Comparator group: 66 • **Loss to follow-up** 3 patients lost to follow up. One patient had a history of penicillin sensitivity, one died postoperatively of peritonitis, and in one case no note was made concerning the state of the wound at the time sutures were removed.
Interventions	• **Vancomycin powder** A corrugated plastic drain was inserted into the peritoneal cavity in cases with severe local peritonitis or generalised peritonitis due to perforation. The drain was brought out through a separate stab incision some distance away from the wound. A phial (500mg) of powder was emptied into the muscle layers after closing peritoneum. Systemic ampicillin was given only in cases of gross peritoneal contamination and peritonitis. No other antibiotics were given for wound infection.
Comparator	• **Placebo** A corrugated plastic drain was inserted into the peritoneal cavity in cases with severe local peritonitis or generalised peritonitis due to perforation. The drain was brought out through a separate stab incision some distance away from the wound. A phial(500mg) of placebo (lactose powder) was emptied into the muscle layers after closing peritoneum. Systemic ampicillin was given only in cases of gross peritoneal contamination and peritonitis. No other antibiotics were given for wound infection.
Outcome measure(s)	• **SSI** In deciding one state of the wound postoperatively, the criteria of Ljungqvist (1964) was adopted. Wound was infected if at any time a purulent discharge appeared. If a serious discharge appeared it was swabbed, cultured, and classified according to results of culture.

Item	Rickett (1969)
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias Insufficient information provided. **Overall risk of bias** • Moderate Unclear random sequence generation and blinding of outcome assessment. **Directness** • Directly applicable

E.23 Rutkowski 2014

Item	Rutkowski (2014)
Title	Surgical site infections following short-term radiotherapy and total mesorectal excision: results of a randomized study examining the role of gentamicin collagen implant in rectal cancer surgery
	Study type • Randomised controlled trial • **Study location**

Item	Rutkowski (2014)
	Poland • **Study setting** Department of Oncological gastroenterology • **Study dates** January 2008 to September 2011. • **Duration of follow-up** 90 days after operation. • **Sources of funding** Grant from the Ministry of Science and Higher Education Republic of Poland. **Inclusion criteria** • Pathology confirmed adenocarcinoma of the rectum located up to 12 cm from the anal verge • aged 18 years and over • World Health Organisation (WHO) performance score 0-1 • no distant metastases • cancer stage cT3-4, N0-2 or cT2 N1-2 • Preoperative short term radiotherapy with 5x5 Gy • Adequate results of blood count: leukocytes equal to or greater than 3.5x 10 ^9/ L, neutrophils/granulocytes equal to or greater than 1.5 x10^9/L and haemoglobin equal to or greater than 9.0 g/dL. **Exclusion criteria** • Presence of distant metastases • Other primary cancer • allergy to gentamicin or collagen • pregnancy • Concomitant disorders such as ulcerative colitis or Crohn's disease. • **Sample size** 176 **Sample characteristics** • **Split between study groups** Intervention group: 86 Comparator group: 85 • **Loss to follow-up** Not specified

Item	Rutkowski (2014)
	• **%female** Intervention group: 35% Comparator group: 31% • **Median age (range)** Intervention group: 63 (38-84) Comparator group: 63 (25-83)
Interventions	• **Gentamicin collagen sponge** The gentamicin collagen implant (Garamycin Innocoll, Athlone, Co., Westmeath, Ireland) contained 130 mg of gentamicin. In all patients, antibiotic prophylaxis was administered.
Comparator	• **No antibiotics** In comparator group, no gentamicin collagen sponge was placed. In all patients, antibiotic prophylaxis was administered.
Outcome measure(s)	• **SSI** Infections classified according to CDC definitions. • **Superficial and/or deep incisional SSI** Infections classified according to CDC definitions. • **Organ/space SSI** Infections classified according to CDC definitions. In this study organ space SSIs were classified as intra-abdominal or intrapelvic abscess and/or peritonitis with or without clinically diagnosed anastomotic leakage. The diagnosis of anastomotic leakage was based on digital rectal examination or observation of faecal material in the drain and confirmed radiologically in CT pelvic scan or by laparotomy.
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Balanced randomisation list was used. No further information was provided. **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Low risk of bias

Item	Rutkowski (2014)
	Selective reporting • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate Unclear random sequence generation and blinding of outcome assessment. **Directness** • Directly applicable

E.24 Rutten 1997

Item	Rutten (1997)
Title	Prevention of wound infection in elective colorectal surgery by local application of a gentamicin-containing collagen sponge
	Study type • Randomised controlled trial • **Study location** The Netherlands • **Study setting** Department of Gastrointestinal surgery • **Study dates** May 1992 and May 1994 • **Duration of follow-up** Not specified. • **Sources of funding** Not specified. **Inclusion criteria** • All patients who underwent elective colorectal surgery.

Item	Rutten (1997)
	Exclusion criteria • Patients undergoing acute operations • Patients who are severely ill/ debilitated condition • Presence of gross contamination. • **Sample size** 221 **Sample characteristics** • **Split between study groups** Intervention: 107 Comparator: 114 • **Loss to follow-up** Not reported • **%female** Intervention: 54% Comparator: 45% • **Mean Age** Intervention: 62.9 Comparator: 63.0
Interventions	• **Gentamicin collagen sponge** Gentamicin collagen sponge was placed upon the closed fascia and directly adjacent to the surgical wound. All patients' received a standard regimen or preoperative bowel preparation and systemic antibiotic therapy.
Comparator	• **No antibiotics** No gentamicin sponge All patients' received a standard regimen or preoperative bowel preparation and systemic antibiotic therapy.
Outcome measure(s)	• **SSI** Follow up assumed to be during the postoperative phase. Wounds were assessed for evidence of infection and discharge fluids underwent microbiological examination for bacterial infection.
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided.

Item	Rutten (1997)
	Allocation concealment • Low risk of bias **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate Unclear random sequence generation and blinding of outcome assessment. **Directness** • Partially directly applicable Follow-up period but specified.

E.25 Schimmer 2012

Item	Schimmer (2012)
Title	Gentamicin-collagen sponge reduces sternal wound complications after heart surgery: a controlled, prospectively randomized, double-blind study
	Study type • Randomised controlled trial • **Study location** Germany

Item	Schimmer (2012)

	• **Study setting**
	Single centre
	• **Study dates**
	June 2009 to June 2010
	• **Duration of follow-up**
	1 month (30 days)
	• **Sources of funding**
	Authors stated that the study was supported by medical device manufacturers: RESORBAW undversorgung GmbH & Co KG
	
	Inclusion criteria
	• People over 18 years old undergoing elective or emergency cardiac surgery (first or resternotomy) with no preoperative signs of thoracic inflammation were included.
	
	Exclusion criteria
	• existing osteitis
	• receiving immunosuppressive therapy or concurrent immunologic disease
	• known hypersensitivity to aminoglycosides
	• pregnancy or lactation
	
	• **Sample size**
	800 participants
	
	Sample characteristics
	• **Split between study groups**
	intervention group = 249;
	comparator group = 284
	• **Loss to follow-up**
	intervention group = 47;
	comparator group = 33
	• **%female**
	intervention group 29.5%;
	comparator group 22.6%
	• **Median age (range)**
	intervention group, 69 years (33-85 years);

Item	Schimmer (2012)
	comparator group, 69 years (29-87 years) • **Body Mass Index (SD)** intervention group, 28.1 (4.5); comparator group, 28.1 (4.3) • **Diabetes (%)** intervention group, 28.0%; comparator group, 32.4% • **COPD (%)** intervention group, 14.2%; comparator group, 13.4%
Interventions	• **Gentamicin collagen sponge** Each patient received perioperative prophylaxis with cefuroxime. After complete adaption of the pericardium and preliminary placement of the sternal wiring, a gentamicin collagen sponge (containing 1.0-1.43 mg gentamicin) was implanted retrosternally, without pre-moistening. Sternal wiring was then performed and the wound was then closed in layers by sutures.
Comparator	• **Placebo** Each patient received perioperative prophylaxis with cefuroxime. After complete adaption of the pericardium and preliminary placement of the sternal wiring, a placebo sponge, identical to the intervention sponge, was implanted retrosternally, without premoistening. Sternal wiring was then performed and the wound was then closed in layers by sutures.
Outcome measure(s)	• **SSI** as defined by the CDC • **Superficial SSI** as defined by the CDC • **Deep SSI** as defined by the CDC
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment**

Item	Schimmer (2012)
	• Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • High risk of bias 80 participants across both study arms were excluded from analyses due to revision surgery, perioperative mortality and non-use of the allocated sponge. No intention to treat analysis was performed. **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • High Unclear random sequence generation, allocation concealment and blinding of outcome assessment. Intention to analysis not performed. **Directness** • Directly applicable

E.26 Sherlock 1984

Item	Sherlock (1984)
Title	Combined preoperative antibiotic therapy and intraoperative topical povidone-iodine. Reduction of wound sepsis following emergency appendectomy
	Study type • Randomised controlled trial • **Study location** UK • **Study setting** Department of surgery. • **Study dates** Not reported • **Duration of follow-up** 4 weeks

Item	Sherlock (1984)
	• **Sources of funding** Not specified. **Inclusion criteria** • Only patients with established perforated or gangrenous appendicitis with or without localised pus. **Exclusion criteria** •Patients who had been given antibiotics prior to hospital admission • Pregnant women • Persons less than 18 years of age. • **Sample size** 75 **Sample characteristics** • **Split between study groups** Intervention group: 39 Comparator group: 36 • **Loss to follow-up** Not reported. • **Age range** 18 to 62 years
Interventions	• **Povidone Iodine** A 10s intraoperative spray of povidone iodine (Disadine) after peritoneal closure. Antibiotic combination (clindamycin and gentamcin) was given one hour preoperatively.
Comparator	• **No antiseptics** No antiseptic was added before skin closure. Antibiotic combination (clindamycin and gentamcin) was given one hour preoperatively.
Outcome measure(s)	• **SSI** According to the observer's findings and results of bacteriologic study, the wounds were divided into three grades: Grade 1: non-infected - primary wound healing, erythema, but no discharge Grade 2: mild infection - erythema of wound with serious discharge; microscopy confirms pus cells, but no growth of pathologic organism Grade 3: Severe infection - Purulent discharge or culture of pathologic organisms in any discharge, with inevitable secondary wound healing.
Risk of bias Directness	**Random sequence generation** • Low risk of bias

Item	Sherlock (1984)
	Allocation concealment • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.27 Tubaki 2013

Item	Tubaki (2013)
Title	Effects of using intravenous antibiotic only versus local intrawound vancomycin antibiotic powder application in addition to intravenous antibiotics on postoperative infection in spine surgery in 907 patients
	Study type • Randomised controlled trial • **Study location** India. • **Study setting** Department of Orthopaedics and Spine Surgery. • **Study dates** June 2011 to December 2012. • **Duration of follow-up**

Item	Tubaki (2013)
	12 weeks. • **Sources of funding** Ganga Orthopaedic Research and Education Foundation. **Inclusion criteria** •Patients undergoing spine surgery. **Exclusion criteria** • Patients with a previous history of infections at the surgical site. • Patients who underwent biopsy procedure. • Patients with a postoperative follow-up time of less than 12 weeks • Patients allergic to vancomycin • Patients undergoing minimal invasive spine surgery. • **Sample size** 907 **Sample characteristics** • **Split between study groups** Intervention Group: 433 Comparator Group: 474 • **Loss to follow-up** Not specified. • **%female** Intervention Group: 56% Comparator Group: 42% • **Mean Age (range)** *Intervention group* Instrumented: 44.5 (3-82) Un-instrumented: 43.7 (12-78) *Comparator group* Instrumented: 46.6 (4-84) Un-instrumented: 46.7 (9-86) • **Diabetes (%)** *Intervention group* Instrumented: 52%

Item	Tubaki (2013)
	Un-instrumented: 23% *Comparator group* Instrumented: 52% Un-instrumented: 25%
Interventions	• **Vancomycin powder** 1 g of vancomycin powder spread throughout the surgical wound. The powder was packed directly on the muscle, fascia, and subcutaneous tissues taking care not to expose bone graft or dura. All patients received standard systemic antibiotic prophylaxis consisting of 750mg of IV cefuroxime.
Comparator	• **No antibiotics** All patients received standard systemic antibiotic prophylaxis consisting of 750mg of IV cefuroxime.
Outcome measure(s)	• **SSI** No information provided on SSI classification criteria. • **Superficial SSI** No information provided on SSI classification criteria. • **Deep SSI** No information provided on SSI classification criteria.
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Unclear risk of bias Unclear if randomisation chart was concealed. **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias**

Item	Tubaki (2013)
	• Unclear risk of bias Insufficient information provided. **Overall risk of bias** • Moderate Unclear allocation concealment and blinding of outcome assessment. **Directness** • Partially directly applicable Criteria used for classification of surgical site infection not specified.

E.28 Walsh 1981

Item	Walsh (1981)
Title	The effect of topical povidone-iodine on the incidence of infection in surgical wounds.
	Study type • Randomised controlled trial • **Study location** Australia • **Study setting** Department of surgery and clinical microbiology. • **Study dates** Not specified. • **Duration of follow-up** 1 month. • **Sources of funding** F.H Faulding and Company for financial support and supplies of povidone iodine (Betadine). **Inclusion criteria** • Patients undergoing abdominal procedures (appendectomy, biliary tract procedures, colonic operations, gastroduodenal operations and miscellaneous procedures). **Exclusion criteria** • None reported

Item	Walsh (1981)
	• **Sample size** 647 **Sample characteristics** • **Split between study groups** Appendectomy Intervention group: 113 Comparator group: 113 Large bowel Intervention group: 22 Comparator group: 19 • **Loss to follow-up** 20 patients were withdrawn due to early death or early reoperation. • **%female** 50% • **Mean Age (range)** 43.4 years (range 6-92 years)
Interventions	• **Povidone Iodine** After closure of the peritoneum, patients were randomly allocated to wound spraying with povidone iodine solution as 5% Betadine (Napp) aerosol spray with 0.5% available iodine). Standard skin preparation with povidone iodine was used throughout the trial, along with standard techniques of wound closure.
Comparator	• **No antiseptics** Standard skin preparation with povidone iodine was used throughout the trial, along with standard techniques of wound closure.
Outcome measure(s)	• **SSI** A wound was considered to be infected if a purulent discharge (with or without bacteriological analysis) appeared at any time within 1 month of operation, or a serosanguinous discharge was positive on culture.
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Unclear risk of bias Insufficient information provided **Blinding of participants and personnel** • High risk of bias Surgeon was informed of the treatment allocation after closure of the peritoneum or the first layer of sutures in the abdominal wall. *However, as outcomes were objective measures, study was not downgraded in this domain.*

Item	Walsh (1981)
	Blinding of outcome assessment • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias Insufficient information provided. **Overall risk of bias** • Low **Directness** • Direct

E.29 Westberg 2015

Item	Westberg (2015)
Title	Effectiveness of gentamicin-containing collagen sponges for prevention of surgical site infection after hip arthroplasty: a multicenter randomized trial
	Study type • Randomised controlled trial • **Study location** Norway • **Study setting** Multicentre (performed across 4 district general hospitals and 1 university hospital) • **Study dates** February 2011 to July 2013 • **Duration of follow-up** 1 month (4 weeks) • **Sources of funding** not reported **Inclusion criteria**

Item	Westberg (2015)
	•People who presented with a displaced femoral neck fracture that was planned to be treated with hemiarthroplasty were eligible for inclusion. **Exclusion criteria** • allergy to gentamicin • ongoing treatment with aminoglycosides • reduced renal function (known renal disease or serum creatinine levels indicating renal dysfunction) • **Sample size** 739 participants **Sample characteristics** • **Split between study groups** intervention group = 366; comparator group = 373 • **Loss to follow-up** 37 participants in the intervention arm, and 18 participants in the comparator arm were excluded from analysis because they did not receive sponges, inclusion errors or losses to follow-up/ • **%female** intervention group 68.7%; comparator group, 79.2% • **Mean age (SD)** intervention group 82.0 years (7.6); comparator group, 83.0 years (8.5) • **Body Mass Index (SD)** intervention group 23.4 (3.7); comparator group, 23.0 (3.9) • **Diabetes (%)** intervention group 11.2% ; comparator group, 11.5%
Interventions	• **Gentamicin collagen sponge** All participants received systemic antibiotic prophylaxis using cephalothin or clindamycin. Following hemiarthroplasty, 1 collagen sponge, containing 130 mg gentamicin sulphate, was placed in the joint and another beneath the fascia. The sponges were placed without premoistening before wound closure.

Item	Westberg (2015)
Comparator	• **No antibiotics** All participants received systemic antibiotic prophylaxis using cephalothin or clindamycin. Following hemiarthroplasty, no collagen sponges were placed as investigators believed that they could theoretically act as a medium for bacterial growth.
Outcome measure(s)	• **Superficial SSI** as defined by the CDC • **Deep SSI** as defined by the CDC • **Mortality post surgery** • **Length of hospital stay**
Risk of bias Directness	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

E.30 Yetim 2010

Item	Yetim (2010)
Title	Effect of local gentamicin application on healing and wound infection in patients with modified radical mastectomy: a prospective randomized study

Item	Yetim (2010)
	Study type • Randomised controlled trial • **Study location** Turkey • **Study setting** Department of General Surgery. • **Study dates** June 2006 and June 2009. • **Duration of follow-up** 6 months after surgery • **Sources of funding** Not specified. **Inclusion criteria** • Female patients who were diagnosed with breast cancer and underwent modified radical mastectomy with axillary dissection. **Exclusion criteria** • Patients with inflammatory breast cancer who had neoadjuvant radiotherapy • Patients who had chronic diseases (e.g. diabetes) or immune suppression. • **Sample size** 44 **Sample characteristics** • **Split between study groups** Intervention group: 22 Comparator group: 22 • **Loss to follow-up** Not reported • **Mean age (SD)** Intervention group: 51.38 (2.41) Comparator group: 50.68 (2.17)
Interventions	• **Gentamicin collagen sponge** Group 1 underwent modified radical mastectomy during which Gentacoll was applied to the axillary area and under the flap area of the breast before the closure of the surgical wound. Two pieces of Gentacoll were used for each area, each comprising 10 x10 x0.5cm

Item	Yetim (2010)
	collagen from equine tendons (280 mg) plus gentamicin sulphate (200 mg). Oral or parenteral antibiotic therapy were not given after surgery.
Comparator	• **No antibiotics** Group 2 underwent modified radical mastectomy without the application of the Gentacoll.
Outcome measure(s)	• **SSI** Criteria used to classify infection not specified. • **Length of hospital stay**
Risk of bias Directness	**Random sequence generation** • Unclear risk of bias Insufficient information provided. **Allocation concealment** • Unclear risk of bias Insufficient information provided. **Blinding of participants and personnel** • Unclear risk of bias Insufficient information provided. *However, as outcomes were objective measures, study was not downgraded in this domain.* **Blinding of outcome assessment** • Unclear risk of bias Insufficient information provided. **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias Insufficient information provided. **Overall risk of bias** • Moderate Unclear random sequence generation, allocation concealment and blinding of outcome assessment. **Directness** • Partially directly applicable Criteria used for classification of surgical site infection not specified.

Appendix F – Forest plots

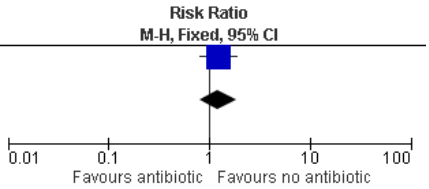
F.1 Erythromycin and colistin-loaded bone cement vs. bone cement without antibiotic

Outcomes at 1 year after surgery

SSI

Study or Subgroup	Antibiotic loaded bone cement Events	Total	No antibiotic Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hinarejos 2013	47	1483	38	1465	100.0%	1.22 [0.80, 1.86]
Total (95% CI)		**1483**		**1465**	**100.0%**	**1.22 [0.80, 1.86]**
Total events	47		38			

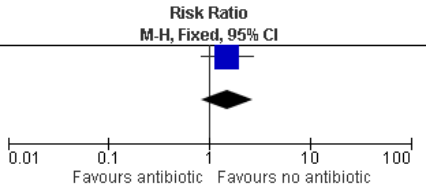
Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)



Superficial SSI

Study or Subgroup	Antibiotic loaded bone cement Events	Total	No antibiotic Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hinarejos 2013	27	1483	18	1465	100.0%	1.48 [0.82, 2.68]
Total (95% CI)		**1483**		**1465**	**100.0%**	**1.48 [0.82, 2.68]**
Total events	27		18			

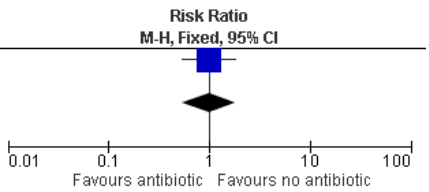
Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)



Deep SSI

Study or Subgroup	Antibiotic loaded bone cement Events	Total	No antibiotic Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hinarejos 2013	20	1483	20	1465	100.0%	0.99 [0.53, 1.83]
Total (95% CI)		**1483**		**1465**	**100.0%**	**0.99 [0.53, 1.83]**
Total events	20		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)

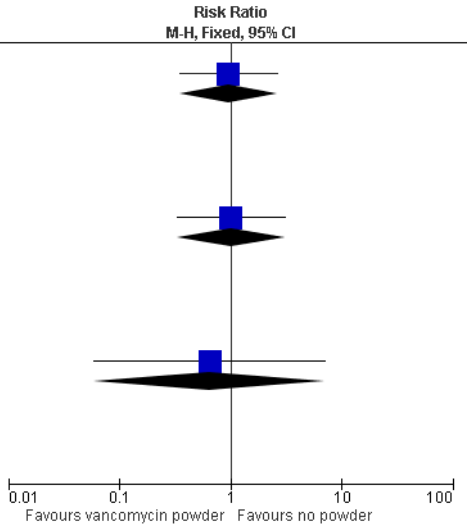


F.2 Vancomycin powder vs no vancomycin powder

Outcomes at 3 months

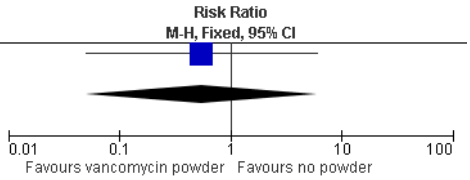
SSI

Study or Subgroup	Vancomycin powder Events	Total	No vancomycin powder Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 All surgeries						
Tubaki 2013 a	7	433	8	474	100.0%	0.96 [0.35, 2.62]
Subtotal (95% CI)		**433**		**474**	**100.0%**	**0.96 [0.35, 2.62]**
Total events	7		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.93)						
2.1.2 Instrumented surgery						
Tubaki 2013 b	6	302	6	304	100.0%	1.01 [0.33, 3.09]
Subtotal (95% CI)		**302**		**304**	**100.0%**	**1.01 [0.33, 3.09]**
Total events	6		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
2.1.3 Non-instrumented surgery						
Tubaki 2013 c	1	131	2	170	100.0%	0.65 [0.06, 7.08]
Subtotal (95% CI)		**131**		**170**	**100.0%**	**0.65 [0.06, 7.08]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.72)						



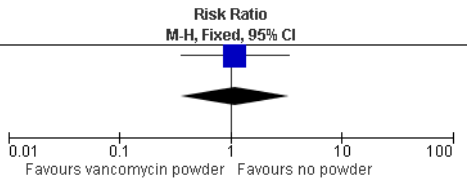
Superficial SSI

Study or Subgroup	Vancomycin powder Events	Total	No vancomycin powder Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tubaki 2013 a	1	433	2	474	100.0%	0.55 [0.05, 6.01]
Total (95% CI)		**433**		**474**	**100.0%**	**0.55 [0.05, 6.01]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.62)						



Deep SSI

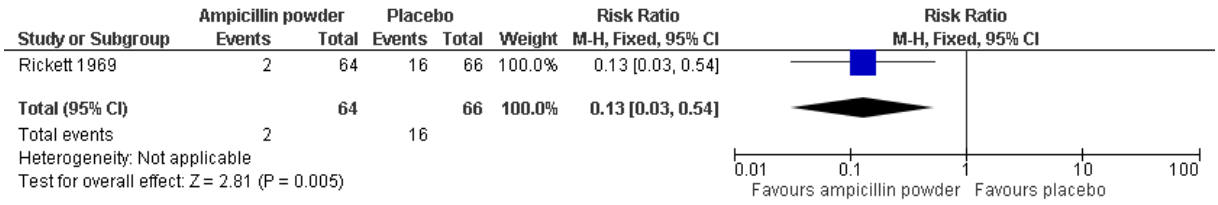
Study or Subgroup	Vancomycin powder Events	Total	No vancomycin powder Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tubaki 2013 a	6	433	6	474	100.0%	1.09 [0.36, 3.37]
Total (95% CI)		**433**		**474**	**100.0%**	**1.09 [0.36, 3.37]**
Total events	6		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						



F.3 Ampicillin powder vs placebo

Outcomes at 3 weeks after surgery

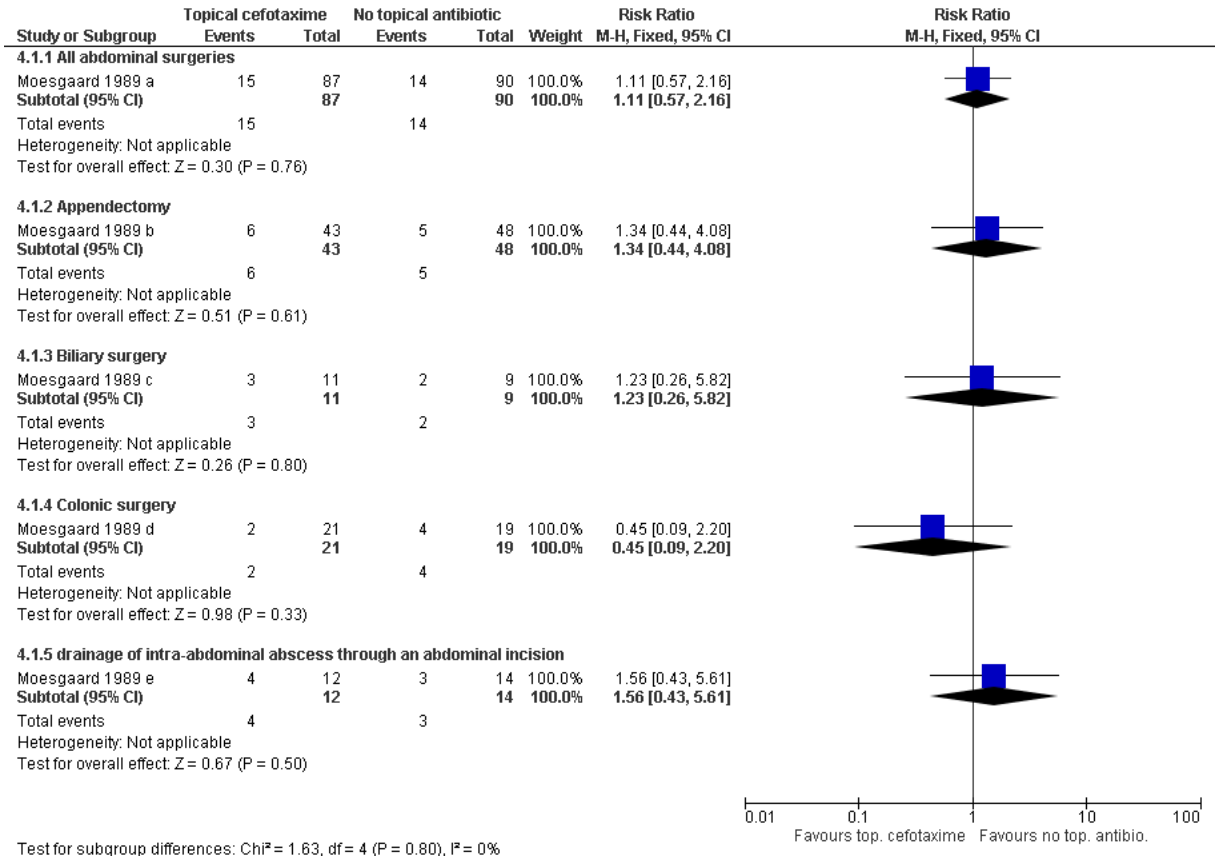
SSI



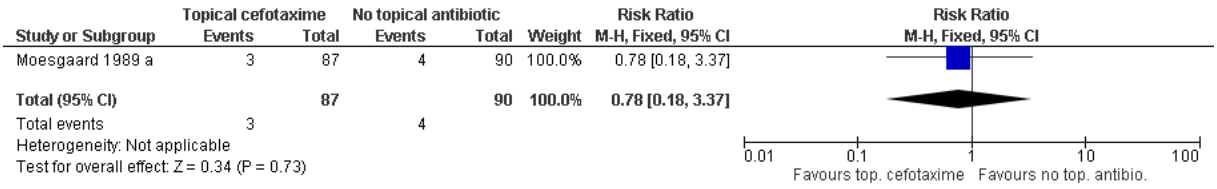
F.4 Topical cefotaxime vs. no topical antibiotic

Outcomes at 1 month after surgery

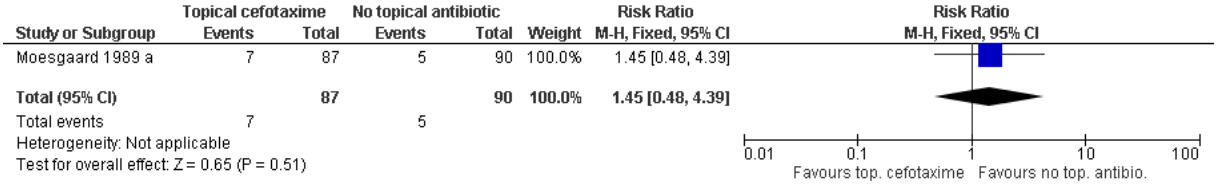
SSI



Septicaemia



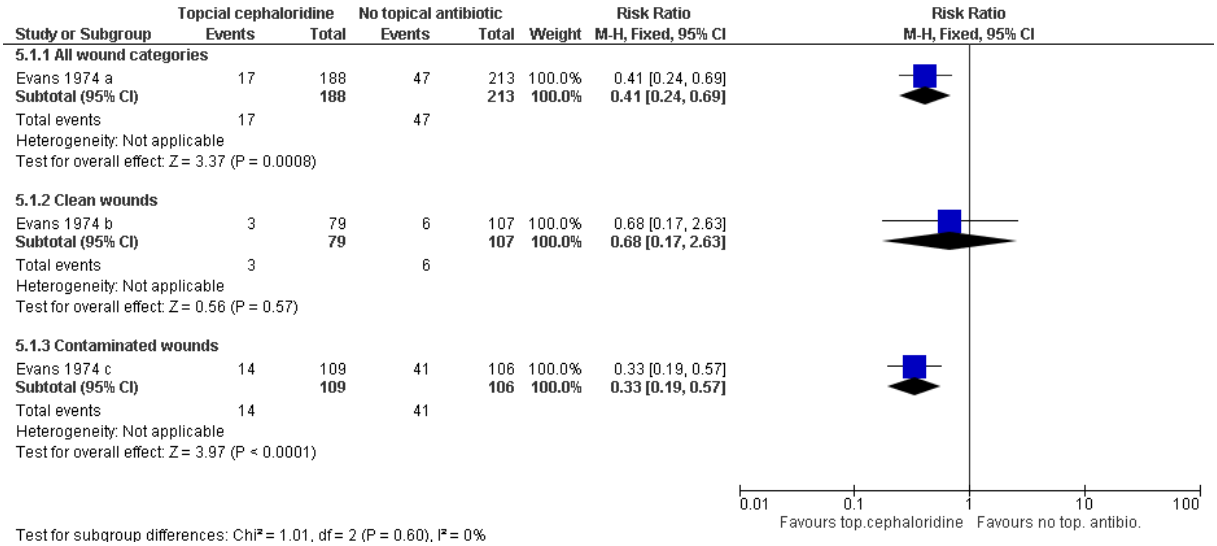
Mortality post-surgery



F.5 Topical cephaloridine vs no topical antibiotic

Outcomes at 1 month after surgery

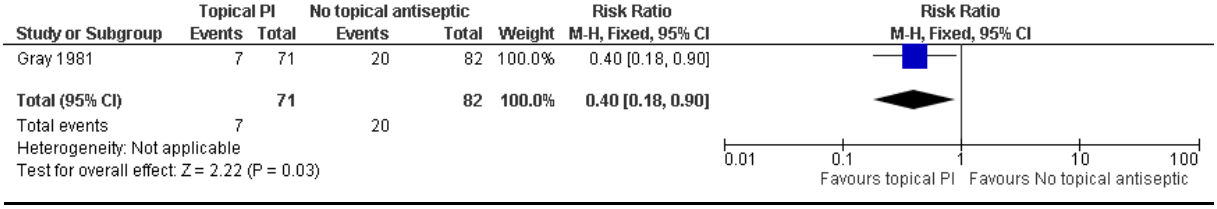
SSI



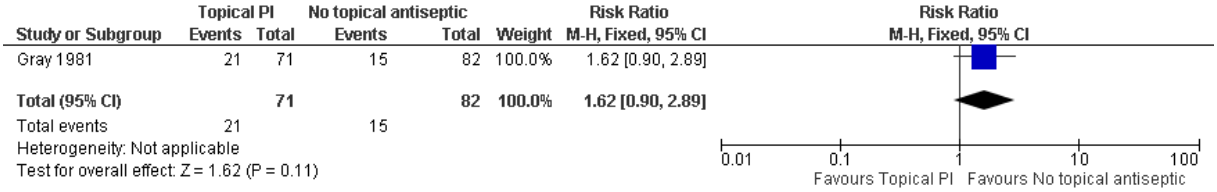
F.6 Topical povidone iodine spray vs no antiseptic spray

Outcomes at 2 weeks after surgery

SSI



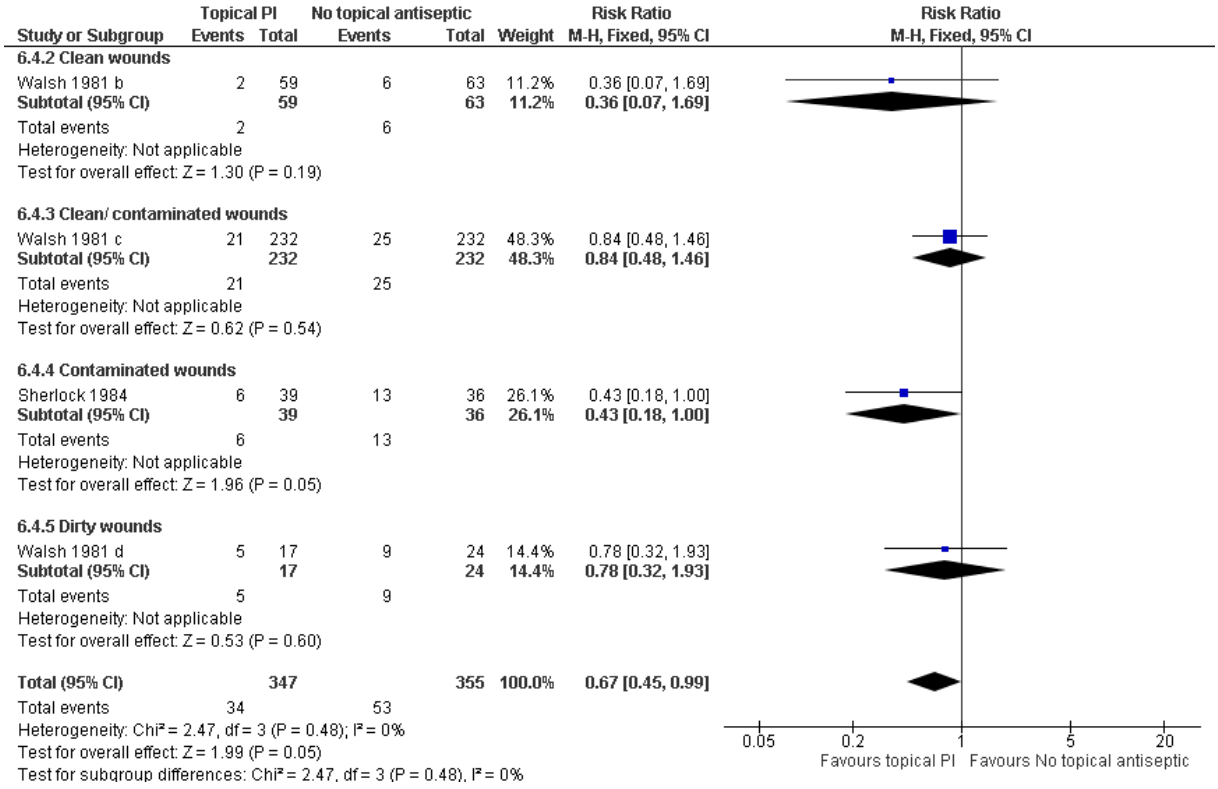
Postoperative antibiotic use



Outcomes at 1 month after surgery

SSI

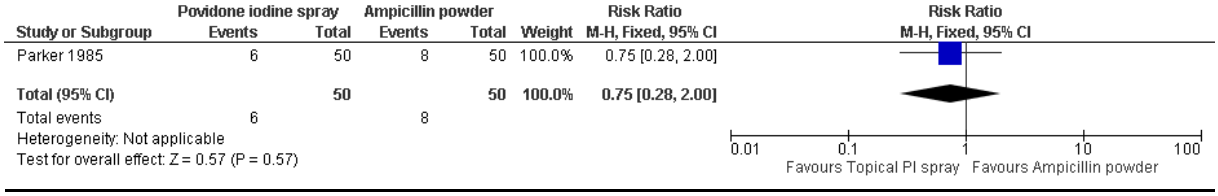
SSI (Analysis by wound category)



F.7 Povidone iodine spray vs ampicillin powder

Outcomes at 1 month after surgery

SSI



F.8 Povidone iodine solution vs no antibiotic solution

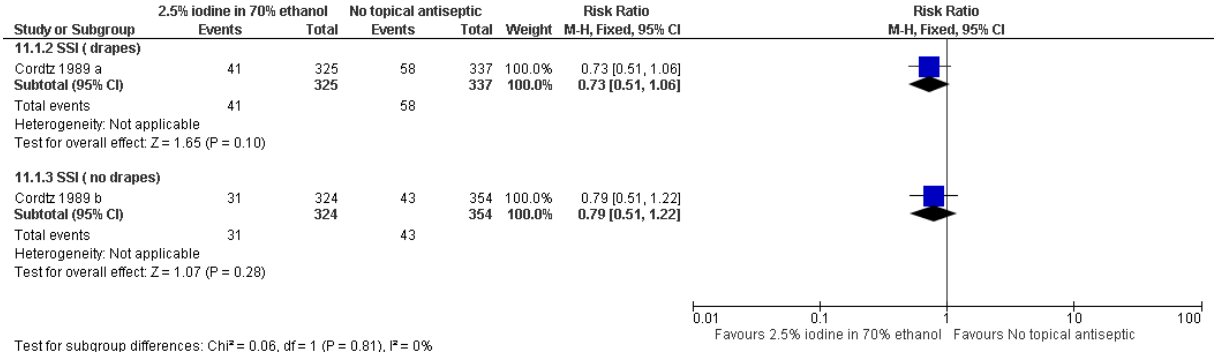
Outcomes during postoperative period

SSI

F.9 Topical 2.5% iodine in 70% ethanol vs no topical antiseptic

Outcomes at 2 weeks

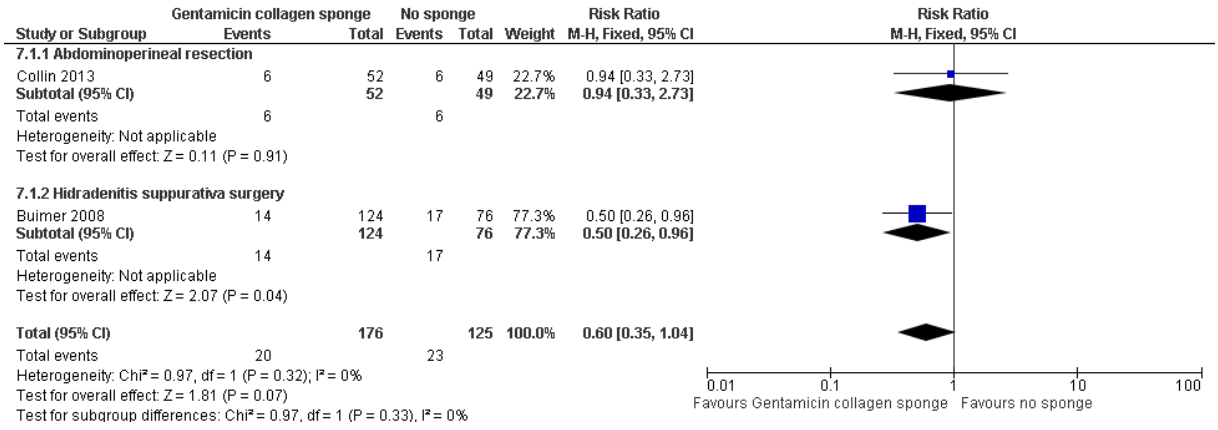
SSI



F.10 Gentamicin collagen sponge vs no sponge

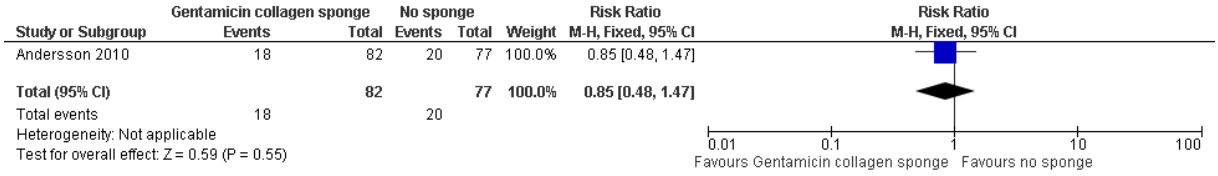
Outcomes at 1 week after surgery

SSI



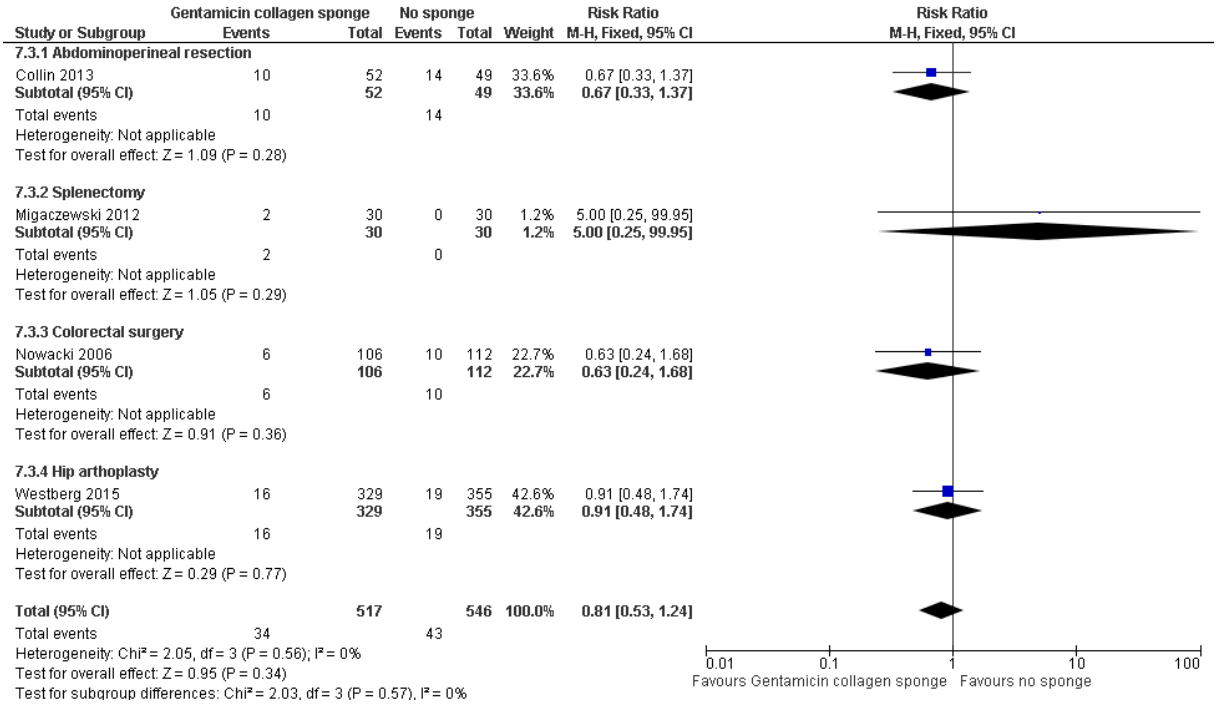
Outcomes at 2 weeks after surgery

SSI

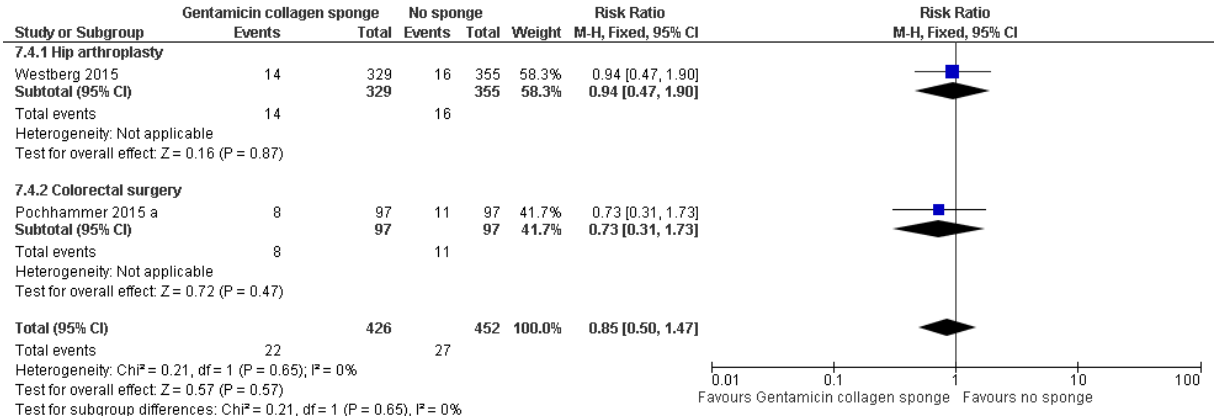


Outcomes at 1 month after surgery

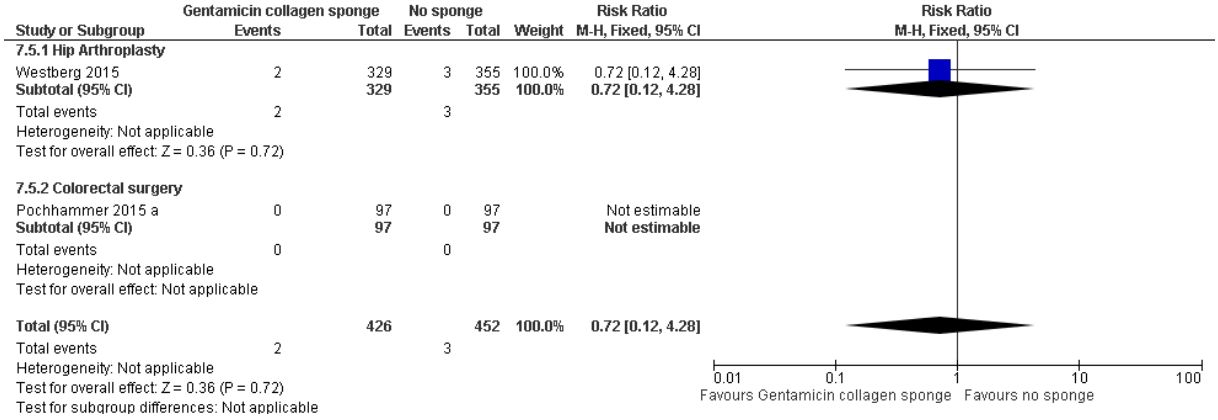
SSI



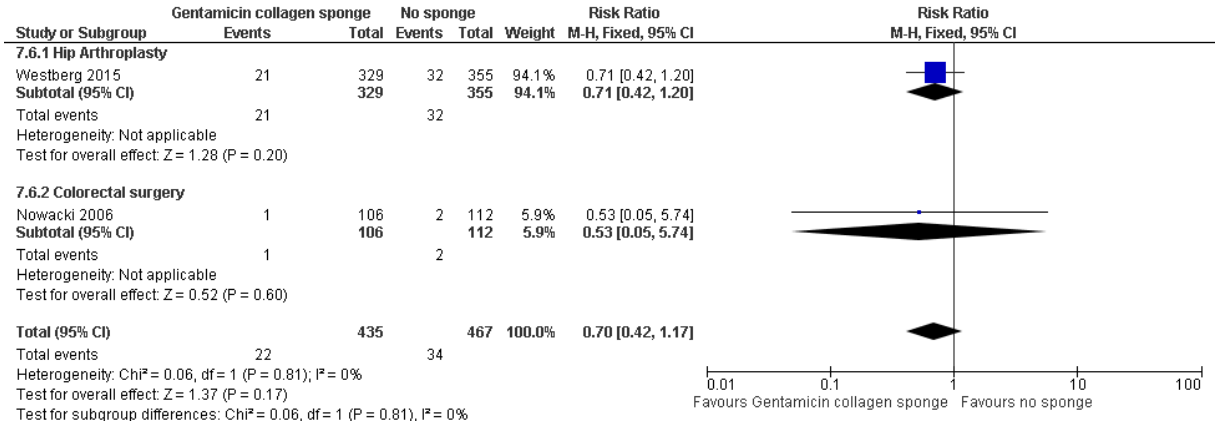
Superficial SSI



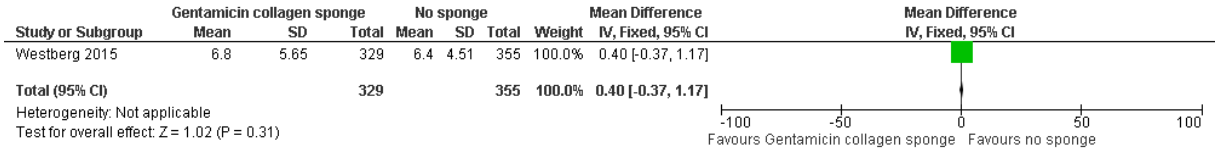
Deep SSI



Mortality post-surgery

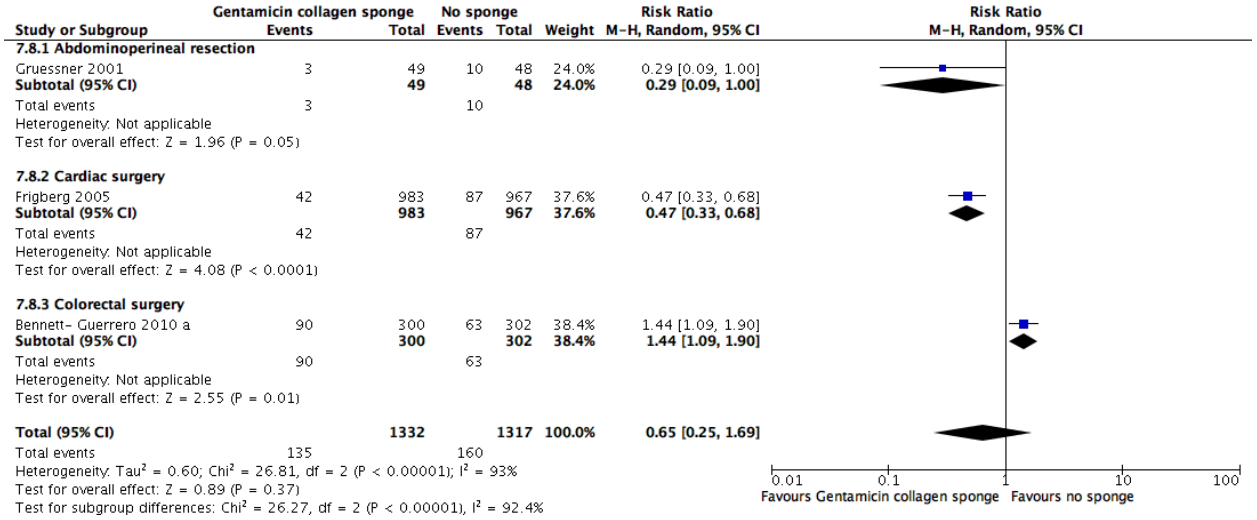


Mean length of stay during 1-month follow up

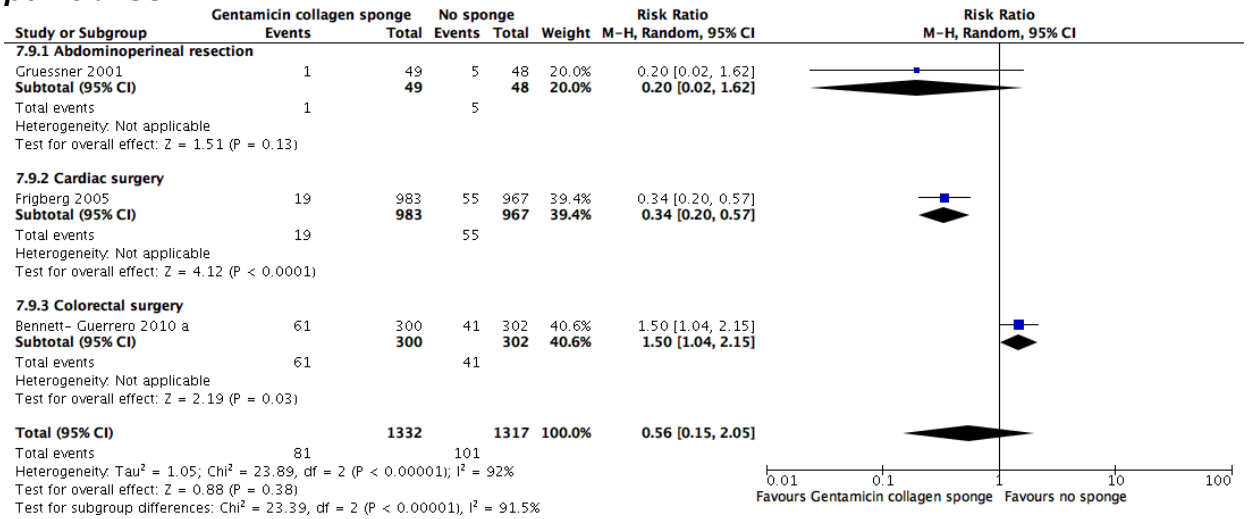


Outcomes at 2 months after surgery

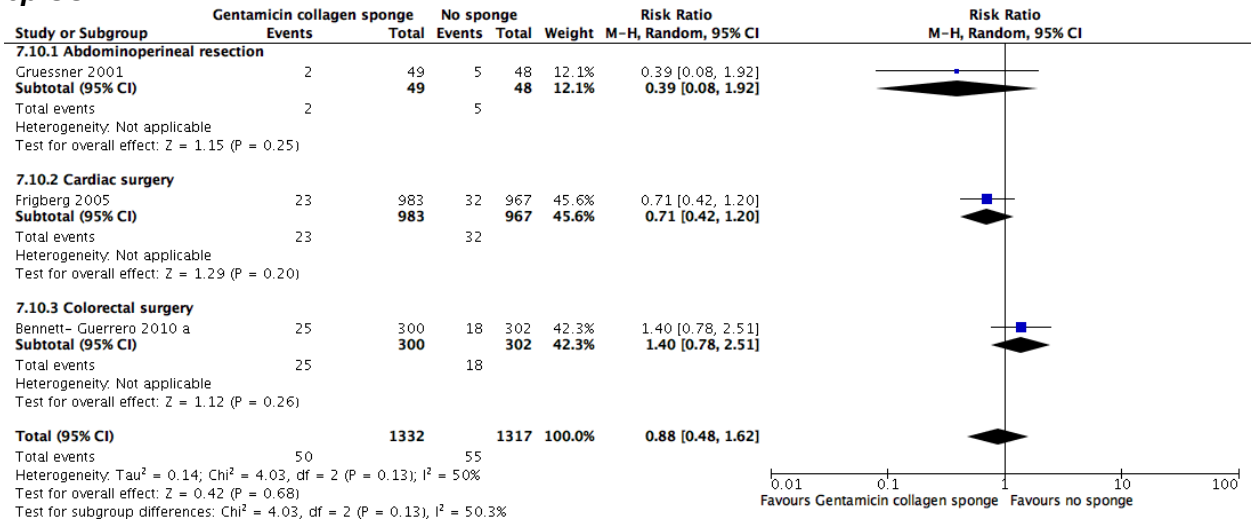
SSI



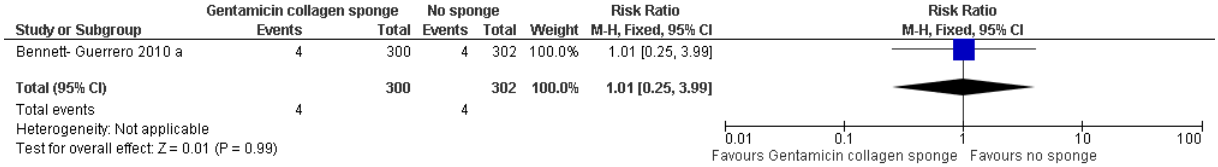
Superficial SSI



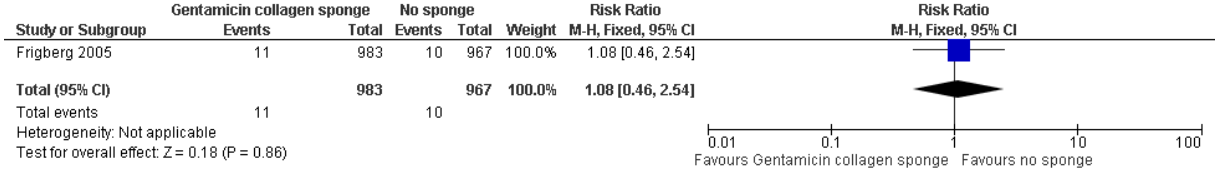
Deep SSI



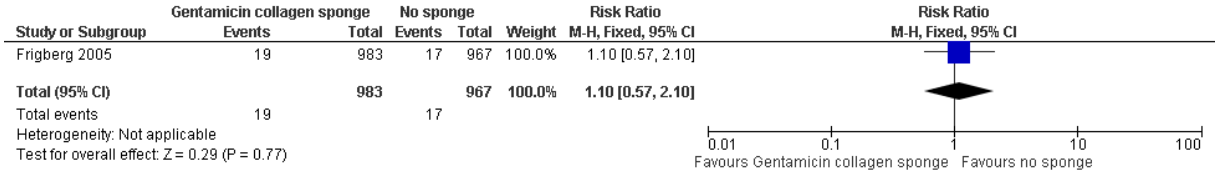
Organ space SSI



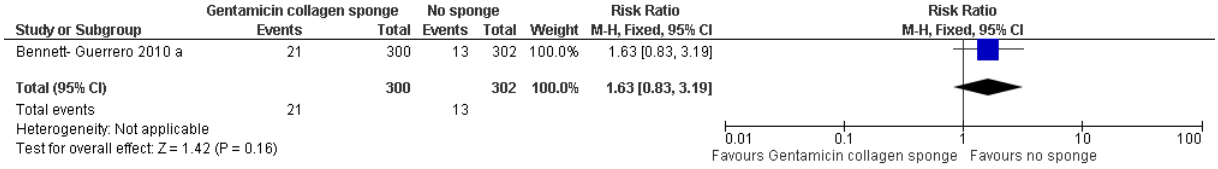
Hospital mortality



Mortality post-surgery

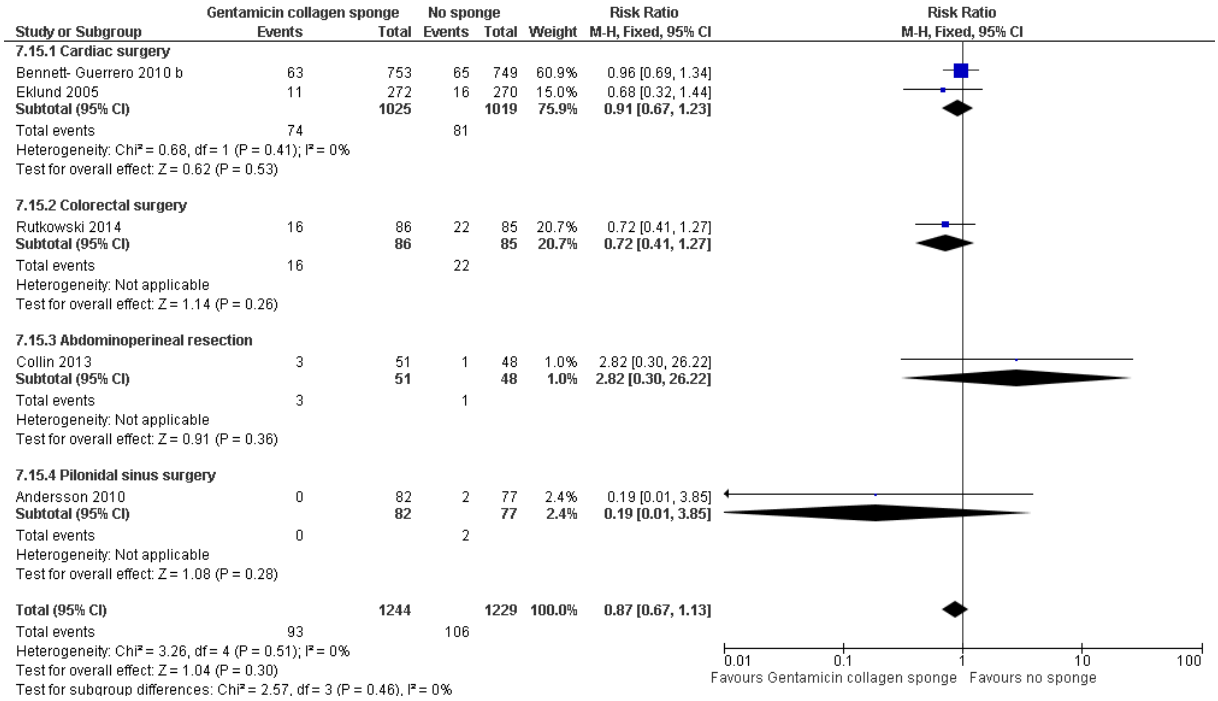


Hospital readmission during 2 month follow up period

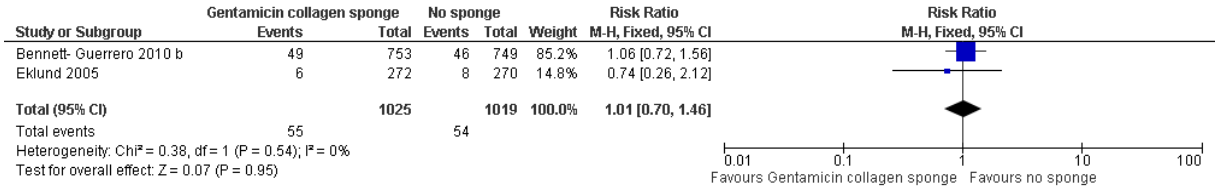


Outcomes at 3 months after surgery

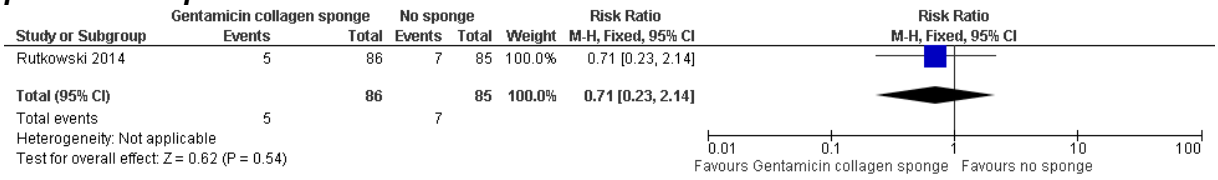
SSI



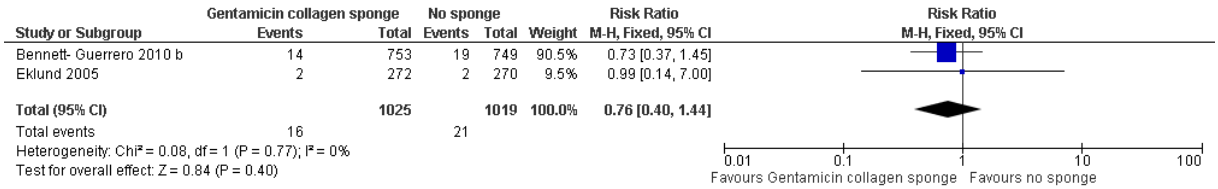
Superficial SSI



Superficial/ deep SSI

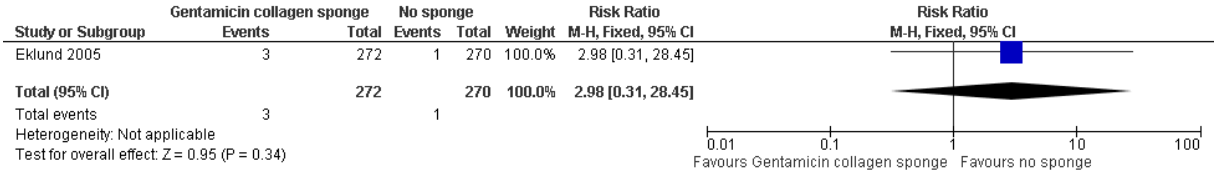


Deep SSI

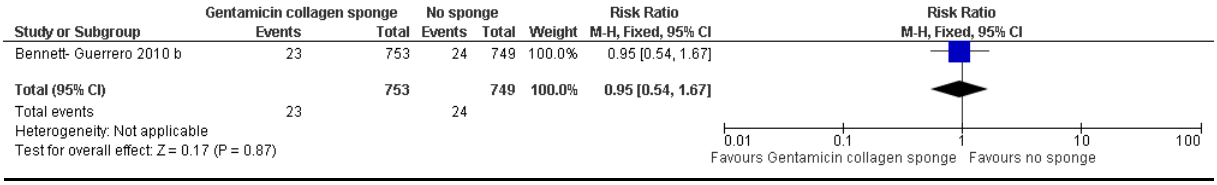


Organ space SSI

Mortality post-surgery

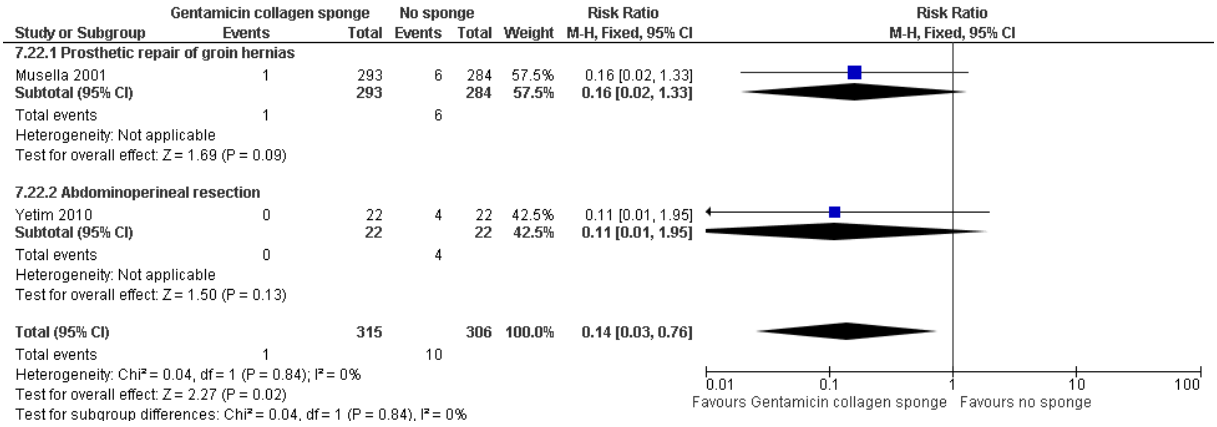


Hospital readmission during 3 month follow up period

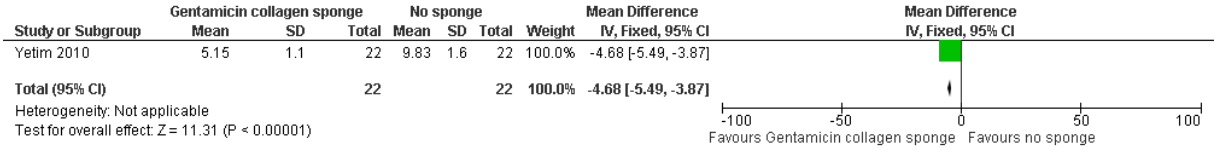


Outcomes at 6 months after surgery

SSI

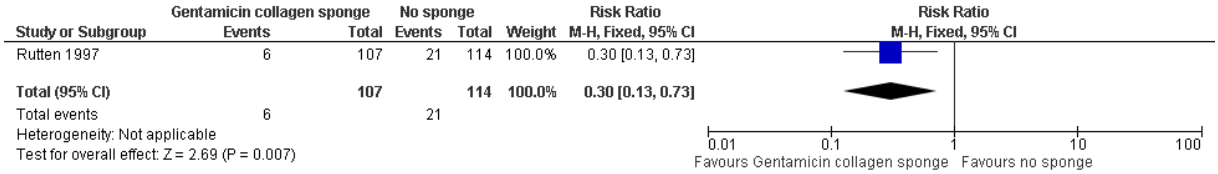


Length of stay



Outcomes during postoperative period

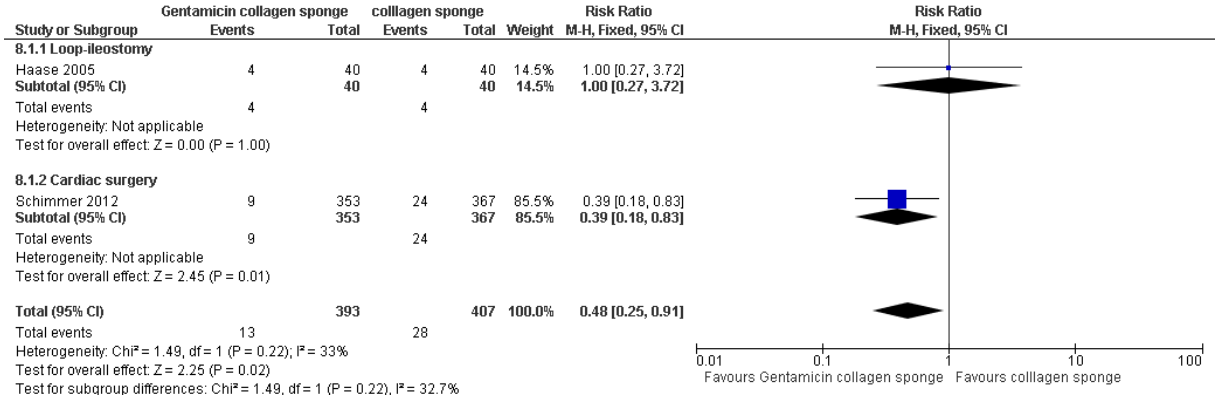
SSI



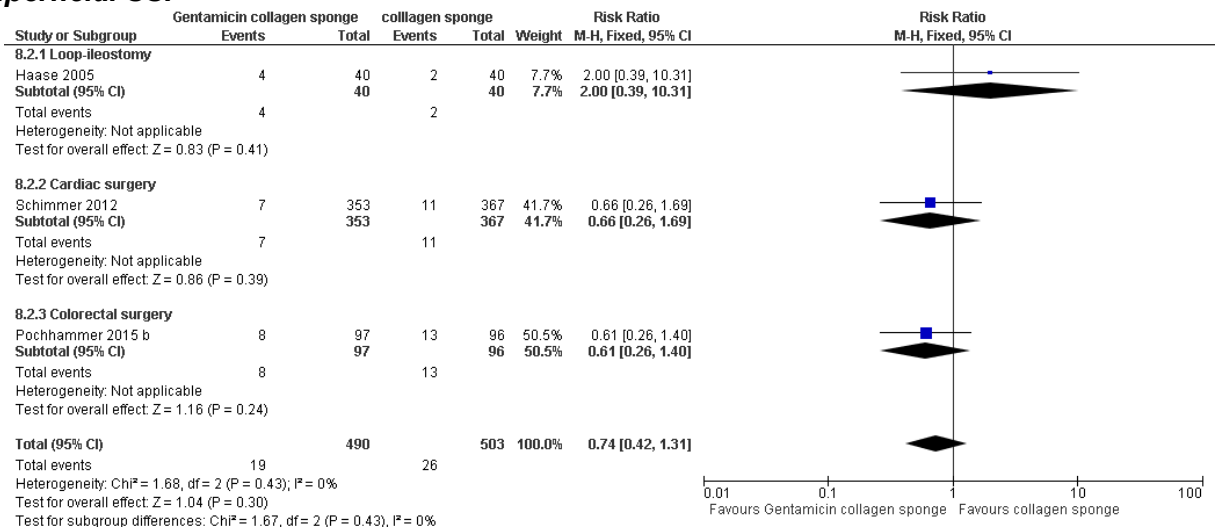
F.11 Gentamicin collagen sponge vs collagen sponge alone

Outcomes at 1 month after surgery

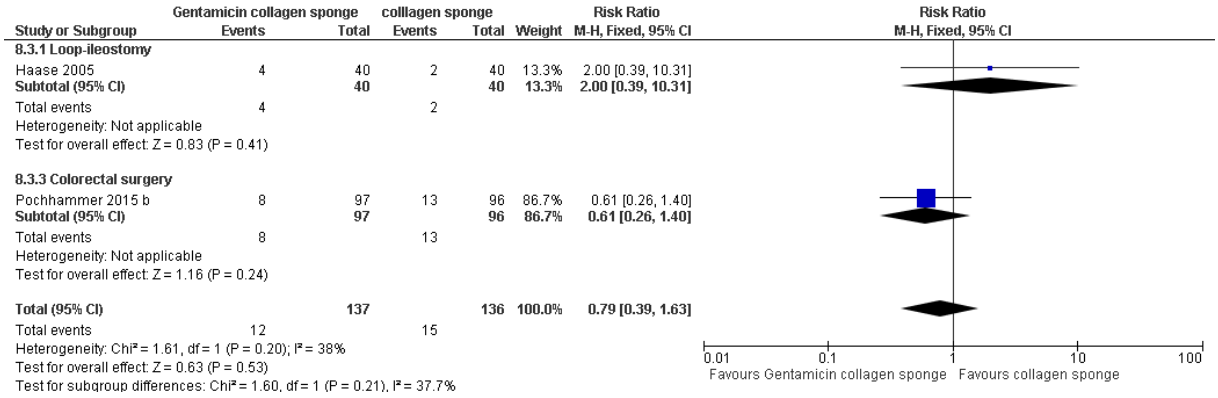
SSI



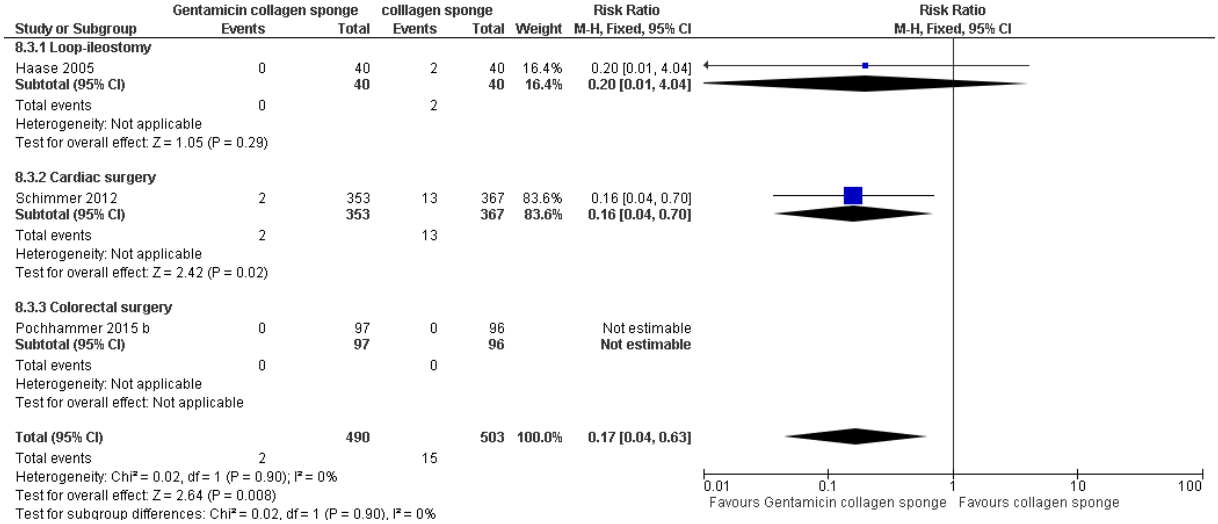
Superficial SSI



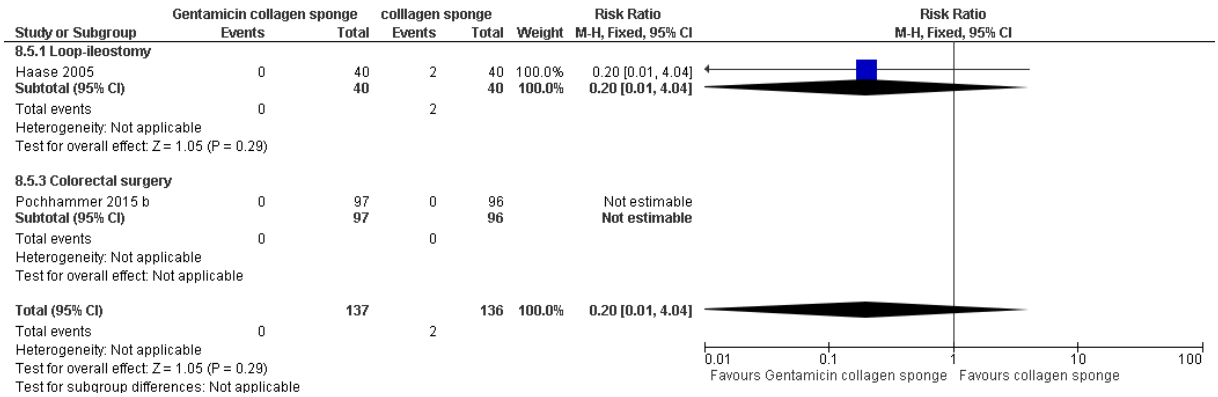
Superficial SSI- Sensitivity analysis (excluding high risk of bias studies)



Deep SSI



Deep SSI- Sensitivity analysis (excluding high risk of bias studies)



Appendix G – GRADE tables

G.1 Erythromycin and colistin loaded bone cement vs. bone cement without antibiotics

Outcomes at 1 year after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours erythromycin and colistin loaded bone cement										
1 Hinarejos 2013	RCT	2948 knees;	RR 1.22 (95% CI: 0.80, 1.86)	3 per 100 knees	3 per 100 knees (2,5)	Serious[1]	Not serious	NA[2]	Very serious[3]	Very low
Superficial SSI - RR <1 favours erythromycin and colistin loaded bone cement										
1 Hinarejos 2013	RCT	2948 knees	RR: 1.48 (95% CI: 0.82, 2.68)	1 per 100 knees	2 per 100 knees (1,3)	Serious[1]	Not serious	NA[2]	Serious[4]	Low
Deep SSI - RR <1 favours erythromycin and colistin loaded bone cement										
1 Hinarejos 2013	RCT	2948 knees	RR: 0.99 (95% CI: 0.53, 1.83)	1 per 100 knees	1 per 100 knees (1,2)	Serious[1]	Not serious	NA[2]	Very serious[3]	Very low

1. Downgrade 1 level for serious risk of bias. Study demonstrated unclear allocation concealment and blinding of outcome assessment.
2. Inconsistency not applicable
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
4. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

G.2 Vancomycin powder vs no vancomycin powder

Outcomes at 3 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI (all surgeries) - RR <1 favours vancomycin powder										
1 Tubaki 2013	RCT	907	RR 0.96 (95% CI: 0.35, 2.62)	2 per 100 people	2 per 100 people (1,4)	Serious[1]	Serious[2]	NA[3]	Very serious[4]	Very low
SSI (instrumented surgery) - RR <1 favours vancomycin powder										
Tubaki 2013	RCT	606	RR 1.01 (95% CI: 0.33, 3.09)	2 per 100 people	2 per 100 people (1,6)	Serious[1]	Serious[2]	NA[3]	Very serious[4]	Very low
SSI (non-instrumented surgery) - RR <1 favours vancomycin powder										
Tubaki 2013	RCT	301	RR 0.65 (95% CI: 0.06, 7.08)	1 per 100 people	1 per 100 people (1,8)	Serious[1]	Serious[2]	NA[3]	Very serious[4]	Very low
Superficial SSI (all surgeries) - RR <1 favours vancomycin powder										
Tubaki 2013	RCT	907	RR 0.55 (95% CI: 0.05, 6.01)	4 per 1000 people**	2 per 1000 people (0, 25)**	Serious[1]	Serious[2]	NA[3]	Very serious[4]	Very low
Deep SSI (all surgeries) - RR <1 favours vancomycin powder										
Tubaki 2013	RCT	907	RR 1.09 (95% CI: 0.36, 3.37)	1 per 100 people	1 per 100 people (1, 4)	Serious[1]	Serious[2]	NA[3]	Very serious[4]	Very low

1. Downgrade 1 level for serious risk of bias. Study demonstrated unclear allocation concealment and blinding of outcome assessment.
2. Study did not specify criteria used for classification of surgical site infections. Downgrade 1 level for serious indirectness.
3. Inconsistency not applicable
4. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

** Derived by taking the overall number of event/ total number of participants and multiplying by 1000

G.3 Ampicillin powder vs placebo

Outcomes at 3 weeks after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours ampicillin powder										
1 Rickett 1969	RCT	130	RR 0.13 (95% CI: 0.03, 0.54)	24 per 100 people	3 per 100 people (1, 13)	Serious[1]	Not serious	NA[2]	Not serious	Moderate

1. Downgrade 1 level for serious risk of bias. Study demonstrated unclear random sequence generation and blinding of outcome assessment.
2. Inconsistency not applicable

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

G.4 Topical cefotaxime vs no topical antibiotic

Outcomes at 1 month after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI (all abdominal surgeries) - RR <1 favours topical cefotaxime										
1 Moesgaard 1989	RCT	177	RR 1.11 (95% CI: 0.57, 2.16)	16 per 100 people	17 per 100 people (9, 34)	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low
SSI (appendectomy) - RR <1 favours topical cefotaxime										
1 Moesgaard 1989	RCT	91	RR 1.34 (95% CI: 0.44, 4.08)	10 per 100 people	14 per 100 people (5, 43)	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low
SSI (biliary surgery) - RR <1 favours topical cefotaxime										
1 Moesgaard 1989	RCT	20	RR 1.23 (95% CI: 0.26, 5.82)	22 per 100 people	27 per 100 people (6, 129)	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low
SSI (colonic surgery) - RR <1 favours topical cefotaxime										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 Moesgaard 1989	RCT	40	RR 0.45 (95% CI: 0.09, 2.20)	21 per 100 people	9 per 100 people (2, 46)	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low
SSI (drainage of intra-abdominal abscess through an abdominal incision) - RR <1 favours topical cefotaxime										
1 Moesgaard 1989	RCT	26	RR 1.56 (95% CI: 0.43, 5.61)	21 per 100 people	33 per 100 people (9, 120)	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low
Septicaemia (all abdominal surgeries) - RR <1 favours topical cefotaxime										
1 Moesgaard 1989	RCT	177	RR 0.78 (95% CI: 0.18, 3.37)	4 per 100 people	3 per 100 people (1, 15)	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low
Mortality post-surgery (all abdominal surgeries) - RR <1 favours topical cefotaxime										
1 Moesgaard 1989	RCT	177	RR: 1.45 (95% CI: 0.48, 4.39)	6 per 100 people	8 per 100 people (3, 24)	Serious[1]	Not serious	NA[2]	Very Serious[3]	Very low

1. Downgrade1 level for serious risk of bias. Study demonstrated unclear random sequence generation and allocation concealment.
2. Inconsistency not applicable
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

G.5 Topical cephaloridine vs no topical antibiotic

Outcomes 1 month after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours Topical cephaloridine										
1 Evans 1974	RCT	401	RR 0.41 (95% CI: 0.24, 0.69)	22 per 100 people	9 per 100 people (5, 15)	Serious[1]	Not serious	NA[2]	Not serious	Moderate
SSI (clean) - RR <1 favours Topical cephaloridine										
1 Evans 1974	RCT	186	RR 0.68 (95% CI: 0.17, 2.63)	6 per 100 people	4 per 100 people (1,15)	Serious[1]	Not serious	NA[2]	Very serious[3]	Very low
SSI (contaminated) - RR <1 favours Topical cephaloridine										
1 Evans 1974	RCT	215	RR: 0.33 (95% CI: 0.19, 0.57)	39 per 100 people	13 per 100 people (7, 22)	Serious[1]	Not serious	NA[2]	Not serious	Moderate

1. Downgrade 1 level for serious risk of bias. Study demonstrated unclear allocation concealment and other sources of bias.
2. Inconsistency not applicable
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

G.6 Topical povidone iodine spray vs no topical antiseptic spray

Outcomes at 2 weeks after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI- RR <1 favours topical povidone iodine spray										
1 Gray 1981	RCT	153	RR 0.40 (95% CI: 0.18, 0.90)	24 per 100 people	10 per 100 people (4, 22)	Not serious	Not serious	NA[1]	Serious[2]	Moderate
Postoperative antibiotic use - RR <1 favours topical povidone iodine spray										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 Gray 1981	RCT	153	RR 1.62 (95% CI: 0.90, 2.89)	18 per 100 people	30 per 100 people (16, 53)	Not serious	Not serious	NA[1]	Serious[2]	Moderate

1. Inconsistency not applicable
2. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Outcomes at 1 month after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours topical povidone iodine spray										
2 Sherlock 1984 Walsh 1981	RCT	702	RR 0.65 (95% CI: 0.43, 0.97)	15 per 100 people	10 per 100 people (6, 14)	Not serious	Not serious	Not serious	Serious[2]	Moderate
SSI (clean) - RR <1 favours topical povidone iodine spray										
1 Walsh 1981	RCT	122	RR 0.36 (95% CI: 0.07, 1.69)	10 per 100 people	3 per 100 people (1, 16)	Not serious	Not serious	NA[1]	Very serious[3]	Low
SSI (clean/ contaminated) - RR <1 favours topical povidone iodine spray										
1 Walsh 1981	RCT	464	RR 0.84 (95% CI: 0.48, 1.46)	11 per 100 people	9 per 100 people (5, 16)	Not serious	Not serious	NA[1]	Very serious[3]	Low
SSI (contaminated) - RR <1 favours topical povidone iodine spray										
1 Sherlock 1984	RCT	75	RR 0.43 (95% CI: 0.18,1.00)	36 per 100 people	16 per 100 people (7, 36)	Not serious	Not serious	NA[1]	Serious[2]	Moderate
SSI (dirty wounds) - RR <1 favours topical povidone iodine spray										
1	RCT	41	RR 0.78 (95% CI: 0.32, 1.93)	38 per 100 people	29 per 100 people (12, 72)	Not serious	Not serious	NA[1]	Very serious[3]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Walsh 1981										

1. Inconsistency not applicable
2. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Povidone iodine spray vs ampicillin powder

Outcomes at 1 month after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI (appendectomy) - RR <1 favours povidone iodine spray										
Parker 1985	RCT	100	RR 0.75 (95% CI: 0.28, 2.00)	16 per 100 people	12 per 100 people (4, 32)	Very Serious[1]	Not serious	NA[2]	Very serious[3]	Very low

1. Downgrade 2 levels for very serious risk of bias. Study demonstrates unclear random sequence generation and allocation concealment. Furthermore, interim outcomes were reported were reported by patients, unclear if patients were blinded.
2. Inconsistency not applicable
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

G.7 Povidone iodine solution vs no antibiotic solution

Outcomes during postoperative period

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours povidone iodine solution										
Harihara 2006	RCT	107	RR 0.98 (95% CI: 0.40, 2.42)	15 per 100 people	15 per 100 people (6, 37)	Serious[1]	Serious[2]	NA[3]	Very serious[4]	Very low

1. Downgrade 1 levels for serious risk of bias. Study demonstrates unclear random sequence generation, allocation concealment and blinding outcome assessment.
2. Downgrade 1 level for serious indirectness. Study did not specify length of follow up.
3. Inconsistency not applicable
4. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

G.8 Topical 2.5% iodine in 70% ethanol vs no topical antiseptic

Outcomes at 2 week after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI (drapes) - RR <1 favours topical 2.5% iodine in 70% ethanol										
Cordtz 1989	RCT	662	RR 0.73 (95% CI: 0.51, 1.06)	17 per 100 people	13 per 100 people (9, 18)	Serious[1]	Not serious	NA[2]	Serious[3]	Low
SSI (no drapes) - RR <1 favours topical 2.5% iodine in 70% ethanol										
Cordtz 1989	RCT	678	RR 0.79 (95% CI: 0.51, 1.22)	12 per 100 people	10 per 100 people (6, 15)	Serious[1]	Not serious	NA[2]	Serious[3]	Low

1. Downgrade 1 levels for serious risk of bias. Study demonstrates unclear random sequence generation, allocation concealment and blinding of outcome assessment.
2. Inconsistency not applicable
3. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
* Derived by taking the overall number of event/ total number of participants and multiplying by 100										

G.9 Gentamicin collagen sponge vs no sponge

Outcomes at 1 week after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours gentamicin collagen sponge										
2 Collin 2013 Buimer 2008	RCT	301	RR 0.60 (95% CI: 0.35, 1.04)	18 per 100 people	11 per 100 people (6, 19)	Serious[1]	Serious[2]	Not serious	Serious[3]	Very low
SSI (Abdominoperineal resection) - RR <1 favours gentamicin collagen sponge										
1 Collin 2013	RCT	101	RR 0.94 (95% CI 0.33, 2.73)	12 per 100 people	12 per 100 people (4, 33)	Serious[5]	Not serious	NA[4]	Very serious[6]	Very low
SSI (Hidradenitis suppurativa surgery) - RR <1 favours gentamicin collagen sponge										
1 Buimer 2008	RCT	200	RR 0.50 (95% CI 0.26, 0.96)	22 per 100 people	11 per 100 people (6, 21)	Serious[7]	Serious[8]	NA[4]	Serious[3]	Very low

1. Downgrade 1 level for serious risk of bias. Greater than 33.3% of the weight in meta-analysis came from with studies of moderate risk of bias due to unclear random sequence generation, allocation concealment as well as unclear or no blinding of outcome assessment.
2. Downgrade 1 level for serious indirectness. Greater than 33.3% of the weight in meta-analysis came from a partially direct study. Buimer (2008) did not specify criteria used to classify surgical site infection.
3. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
4. Inconsistency not applicable
5. Downgrade 1 level for serious risk of bias. Study demonstrates no blinding of outcome assessment.
6. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
7. Downgrade 1 level for serious risk of bias. Study demonstrates unclear random sequence generation, allocation concealment and blinding of outcome assessment.										
8. Buimer (2008) did not specify criteria used to classify surgical site infections. Downgrade 1 level for serious indirectness.										
* Derived by taking the overall number of event/ total number of participants and multiplying by 100										

Outcomes at 2 weeks after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours gentamicin collagen sponge										
1 Andersson 2010	RCT	159	RR 0.85 (95% CI: 0.48, 1.47)	26 per 100 people	22 per 100 people (12, 38)	Not serious	Serious[1]	NA[2]	Very serious[3]	Very low
1. Andersson (2010) did not explicitly specify criteria used for the classification of surgical site infections. Downgrade 1 level for serious indirectness.										
2. Inconsistency not applicable										
3. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.										
* Derived by taking the overall number of event/ total number of participants and multiplying by 100										

Outcomes at 1 month after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours gentamicin collagen sponge										
4 Collin 2013 Migaczewski 2010 Nowacki 2006	RCT	1,063	RR 0.81 (95% CI: 0.53, 1.24)	8 per 100 people	6 per 100 people (4, 10)	Serious[1]	Not serious	Not serious	Serious[2]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Westberg 2015										
SSI (abdominoperineal resection) - RR <1 favours gentamicin collagen sponge										
1 Collin 2013	RCT	101	RR 0.67 (95% CI 0.33, 1.37)	29 per 100 people	19 per 100 people (9, 39)	Serious[3]	Not serious	NA[4]	Very serious[5]	Very low
SSI (splenectomy) - RR <1 favours gentamicin collagen sponge										
1 Migaczewski 2012	RCT	60	RR 5.00 (95% CI: 0.25, 99.95)	Not calculable[11]	Not calculable[11]	Serious[6]	Serious[7]	NA[4]	Very serious[5]	Very low
SSI (colorectal surgery) - RR <1 favours gentamicin collagen sponge										
1 Nowacki 2006	RCT	218	RR 0.63 (95% CI: 0.24, 1.68)	9 per 100 people	6 per 100 people (2, 15)	Serious[6]	Serious[7]	NA[4]	Very serious[5]	Very low
SSI (hip arthroplasty) - RR <1 favours gentamicin collagen sponge										
1 Westberg 2015	RCT	684	RR 0.91 (95% CI: 0.48, 1.74)	5 per 100 people	5 per 100 people (3, 9)	Not serious	Not serious	NA[4]	Very Serious[5]	Low
Superficial SSI - RR <1 favours gentamicin collagen sponge										
2 Westberg 2015 Pochammer 2015	RCT	878	RR 0.85 (95% CI: 0.50, 1.47)	6 per 100 people	5 per 100 people (3, 9)	Not serious	Not serious	Not serious	Very serious[5]	Low
Superficial SSI (Hip arthroplasty) - RR <1 favours gentamicin collagen sponge										
1 Westberg 2015	RCT	684	RR 0.94 (95% CI: 0.47, 1.90)	5 per 100 people	4 per 100 people (2, 9)	Not serious	Not serious	NA[4]	Very serious[5]	Low
Superficial SSI (colorectal surgery) - RR <1 favours gentamicin collagen sponge										
1 Pochammer 2015	RCT	194	RR 0.73 (95% CI: 0.31, 1.73)	11 per 100 people	8 per 100 people (4, 20)	Not serious	Not serious	NA[4]	Very serious[5]	Low
Deep SSI - RR <1 favours gentamicin collagen sponge										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
2 Westberg 2015 Pochammer 2015	RCT	878	RR 0.72 (95% CI: 0.12, 4.28)	1 per 100 people	1 per 100 people (0, 2)	Not serious	Not serious	Not serious	Very serious[5]	low
Deep SSI (hip arthroplasty) - RR <1 favours gentamicin collagen sponge										
1 Westberg 2015	RCT	684	RR 0.72 (95% CI: 0.12, 4.28)	1 per 100 people	1 per 100 people (0, 2)	Not serious	Not serious	NA[4]	Very serious[5]	low
Deep SSI (colorectal surgery) - RR <1 favours gentamicin collagen sponge										
1 Pochammer 2015	RCT	194	RR not estimable due to no occurrence of event in either study arm.			Not serious	Not serious	NA[4]	Very Serious[8]	Low
Mortality post-surgery - RR <1 favours gentamicin collagen sponge										
2 Westberg 2015 Nowacki 2006	RCT	902	RR 0.70 (95% CI: 0.42, 1.17)	7 per 100 people	5 per 100 people (3, 9)	Not serious	Not serious	Not serious	Serious[2]	Moderate
Mortality post-surgery (Hip arthroplasty) - RR <1 favours gentamicin collagen sponge										
1 Westberg 2015	RCT	684	RR 0.71 (95% CI: 0.42, 1.20)	9 per 100 people	6 per 100 people (4, 11)	Not serious	Not serious	NA[4]	Serious[2]	Moderate
Mortality post-surgery (colorectal surgery) - RR <1 favours gentamicin collagen sponge										
1 Nowacki 2006	RCT	218	RR 0.53 (95% CI: 0.05, 5.74)	2 per 100 people	1 per 100 people (0, 10)	Serious[6]	Serious[7]	NA[4]	Very serious[5]	Very low
Mean length of stay – effect size below zero favours gentamicin collagen sponge										
1 Westberg 2015	RCT	684	MD: 0.40 (95% CI: -0.37, 1.17)	-	-	Not serious	Not serious	NA[4]	Serious[9]	Moderate
Length of stay – effect size below zero favours gentamicin collagen sponge										
1 Pochammer 2015	RCT	194	Difference in medians: 0 days (non- significant according to Kurskal-Wallis test)			Not serious	Not serious	NA[4]	Very serious[10]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1. Downgrade 1 level for serious risk of bias. Greater than 33.3% of the weight in meta-analysis came from with studies of moderate risk of bias due to unclear random sequence generation, allocation concealment as well as unclear or no blinding of outcome assessment.
2. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
3. Downgrade 1 level for serious risk of bias. Study demonstrates no blinding of outcome assessment.
4. Inconsistency not applicable
5. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
6. Downgrade 1 level for serious risk of bias. Study demonstrates unclear random sequence generation, allocation concealment and blinding of outcome assessment.
7. Study did not specify criteria used to classify surgical site infections. Downgrade 1 level for serious indirectness.
8. Unable to calculate effect size. Downgrade 2 levels
9. Non-significant result. Downgrade 1 level.
10. Downgrade 2 levels for no measure of spread and non-significant results.
11. The absolute risk was not calculable as there were no events in the control arm.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Outcomes at 2 months after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours gentamicin collagen sponge										
3 Gruessner 2001 Frigberg 2005 Bennett-Guerrero 2010	RCT	2,649	RR 0.65 (95% CI: 0.25, 1.69)	12 per 100 people	8 per 100 people (3, 21)	Not serious	Not serious	Very serious[1]	Very serious[2]	Very Low
SSI (abdominoperineal resection) - RR <1 favours gentamicin collagen sponge										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 Gruessner 2001	RCT	97	RR 0.29 (95% CI: 0.09, 1.00)	21 per 100 people	6 per 100 people (2, 21)	Serious[3]	Serious[4]	NA[5]	Serious[6]	Very low
SSI (cardiac surgery) - RR <1 favours gentamicin collagen sponge										
1 Frigberg 2005	RCT	1950	RR 0.47 (95% CI: 0.33, 0.68)	9 per 100 people	4 per 100 people (3, 6)	Not serious	Not serious	NA[5]	Not serious	High
SSI (colorectal surgery) - RR <1 favours gentamicin collagen sponge										
1 Bennett-Guerrero 2010	RCT	602	RR 1.44 (95% CI: 1.09, 1.90)	21 per 100 people	30 per 100 people (23, 40)	Not serious	Not serious	NA[5]	Serious[6]	Moderate
Superficial SSI - RR <1 favours gentamicin collagen sponge										
3 Gruessner 2001 Frigberg 2005 Bennett-Guerrero 2010	RCT	2,649	RR 0.56 (95% CI: 0.15, 2.05)	8 per 100 people	4 per 100 people (1, 16)	Not serious	Not serious	Very serious[1]	Very serious[2]	Very Low
Superficial SSI (abdominoperineal resection) - RR <1 favours gentamicin collagen sponge										
1 Gruessner 2001	RCT	97	RR 0.20 (95% CI: 0.02, 1.62)	10 per 100 people	2 per 100 people (0, 17)	Serious[3]	Serious[4]	NA[5]	Very serious[2]	Very low
Superficial SSI (cardiac surgery) - RR <1 favours gentamicin collagen sponge										
1 Frigberg 2005	RCT	1950	RR 0.34 (95% CI: 0.20, 0.57)	6 per 100 people	2 per 100 people (1, 3)	Not serious	Not serious	NA[5]	Not serious	High
Superficial SSI (colorectal surgery) - RR <1 favours gentamicin collagen sponge										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 Bennett-Guerrero 2010	RCT	602	RR 1.50 (95% CI: 1.04, 2.15)	14 per 100 people	20 per 100 people (14, 29)	Not serious	Not serious	NA[5]	Serious[6]	Moderate
Deep SSI - RR <1 favours gentamicin collagen sponge										
3 Gruessner 2001 Frigberg 2005 Bennett-Guerrero 2010	RCT	2,649	RR 0.88 (95% CI: 0.48, 1.62)	4 per 100 people	4 per 100 people (2, 7)	Not serious	Not serious	Serious[7]	Very serious[2]	Very low
Deep SSI (abdominoperineal resection) - RR <1 favours gentamicin collagen sponge										
1 Gruessner 2001	RCT	97	RR 0.39 (95% CI: 0.08, 1.92)	10 per 100 people	4 per 100 people (1, 20)	Serious[3]	Serious[4]	NA[5]	Very serious[2]	Very low
Deep SSI (cardiac surgery) - RR <1 favours gentamicin collagen sponge										
1 Frigberg 2005	RCT	1950	RR 0.71 (95% CI: 0.42, 1.20)	3 per 100 people	2 per 100 people (1, 4)	Not serious	Not serious	NA[5]	Serious[6]	Moderate
Deep SSI (colorectal surgery) - RR <1 favours gentamicin collagen sponge										
1 Bennett-Guerrero 2010	RCT	602	RR 1.40 (95% CI: 0.78, 2.51)	6 per 100 people	8 per 100 people (5, 7)	Not serious	Not serious	NA[5]	Very serious[2]	Low
Organ space SSI - RR <1 favours gentamicin collagen sponge										
1 Bennett-Guerrero 2010	RCT	602	RR 1.01 (95% CI: 0.25, 3.99)	1 per 100 people	1 per 100 people (0, 5)	Not serious	Not serious	NA[5]	Very serious[2]	Low
Hospital mortality - RR <1 favours gentamicin collagen sponge										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 Frigberg 2005	RCT	1950	RR 1.08 (95% CI: 0.46, 2.54)	1 per 100 people	1 per 100 people (0, 3)	Not serious	Not serious	NA[5]	Very serious[2]	Low
Mortality post-surgery - RR <1 favours gentamicin collagen sponge										
1 Frigberg 2005	RCT	1950	RR 1.10 (95% CI: 0.57, 2.10)	2 per 100 people	2 per 100 people (1, 4)	Not serious	Not serious	NA[5]	Very serious[2]	Low
Hospital readmission - RR <1 favours gentamicin collagen sponge										
1 Bennett-Guerrero 2010	RCT	602	RR 1.63 (95% CI: 0.83, 3.19)	4 per 100 people	7 per 100 people (4, 14)	Not serious	Not serious	NA[5]	Serious[6]	Moderate
Length of stay – effective size below zero favours gentamicin collagen sponge										
1 Bennett-Guerrero 2010	RCT	602	Difference in medians: 0 days (non- significant according to Chi-square test)			Not serious	Not serious	NA[5]	Very serious [8]	Low

1. Downgrade 2 levels for very serious inconsistency. I^2 was greater than 66.7%.
2. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
3. Downgrade 1 level for serious risk of bias. Study demonstrates unclear random sequence generation, allocation concealment and blinding of outcome assessment.
4. Study did not specify criteria used for the classification of surgical site infections. Downgrade 1 level for partial indirectness.
5. Inconsistency not applicable
6. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
7. Downgrade 1 level for serious inconsistency. I^2 was between 33.3% and 66.7%
8. Downgrade 2 levels for no measure of spread and non-significant results.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Outcomes at 3 months after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours gentamicin collagen sponge										
5 Bennett-Guerrero 2010, Eklund 2005, Rutkowski 2014, Collin 2013, Andersson 2010	RCT	2473	RR 0.87 (95% CI: 0.67, 1.13)	9 per 100 people	8 per 100 people (6, 10)	Not serious	Not serious	Not serious	Serious[1]	Moderate
SSI (cardiac surgery) - RR <1 favours gentamicin collagen sponge										
2 Bennett-Guerrero 2010, Eklund 2005	RCT	2044	RR 0.91 (95% CI: 0.67, 1.23)	8 per 100 people	7 per 100 people (5, 10)	Not serious	Not serious	Not serious	Serious[1]	Moderate
SSI (colorectal surgery) - RR <1 favours gentamicin collagen sponge										
1 Rutkowski 2014	RCT	171	RR 0.72 (95% CI: 0.41, 1.27)	26 per 100 people	19 per 100 people 11, 33)	Serious[3]	Not serious	NA[2]	Very serious[4]	Very low
SSI (Abdominoperineal resection) - RR <1 favours gentamicin collagen sponge										
1 Collin 2013	RCT	99	RR 2.28 (95% CI: 0.30, 26.22)	2 per 100 people	6 per 100 people (1, 55)	Serious[5]	Not serious	NA[2]	Very serious[4]	Very low
SSI (Pilonidal sinus surgery) - RR <1 favours gentamicin collagen sponge										
1 Andersson 2010	RCT	159	RR 0.19 (95% CI: 0.01, 3.85)	3 per 100 people	0 per 100 people (0, 10)	Not serious	Serious[6]	NA[2]	Very serious[4]	Low
Superficial SSI - RR <1 favours gentamicin collagen sponge										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
2 Bennett-Guerrero 2010, Eklund 2005	RCT	2,044	RR 1.01 (95% CI: 0.70, 1.46)	5 per 100 people	5 per 100 people (4, 8)	Not serious	Not serious	Not serious	Very serious[4]	Low
Superficial/ deep SSI - RR <1 favours gentamicin collagen sponge										
1 Rutkowski 2014	RCT	171	RR 0.71 (95% CI: 0.23, 2.14)	8 per 100 people	6 per 100 people (2, 18)	Serious[3]	Not serious	NA[2]	Very serious[4]	Very low
Deep SSI - RR <1 favours gentamicin collagen sponge										
2 Bennett-Guerrero 2010, Eklund 2005	RCT	2,044	RR 0.76 (95% CI: 0.40, 1.44)	2 per 100 people	2 per 100 people (1, 3)	Not serious	Not serious	Not serious	Very serious[4]	Low
Organ space SSI- RR <1 favours gentamicin collagen sponge										
2 Bennett-Guerrero 2010, Eklund 2005	RCT	2,044	RR 0.63 (95% CI: 0.34, 1.18)	6 per 100 people	4 per 100 people (2, 7)	Not serious	Not serious	Not serious	Serious[1]	Moderate
Mortality post-surgery - RR <1 favours gentamicin collagen sponge										
1 Eklund 2005	RCT	542	RR 2.98 (95% CI: 0.31, 28.45)	0 per 100 people	1 per 100 people (0, 11)	Not serious	Not serious	NA[2]	Very serious[4]	Low
Hospital readmission - RR <1 favours gentamicin collagen sponge										
1 Bennett-Guerrero 2010	RCT	1,502	RR 0.95 (95% CI: 0.54, 1.67)	3 per 100 people	3 per 100 people (3, 5)	Not serious	Not serious	NA[2]	Very serious[3]	Low
Length of stay										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 Bennett-Guerrero 2010	RCT	1,502	Difference in medians: 0 days (non- significant according to Chi-square test)			Not serious	Not serious	NA[2]	Very serious[7]	Low

1. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
2. Inconsistency not applicable
3. Downgrade 1 level for serious risk of bias. Study demonstrates unclear random sequence generation and blinding of outcome assessment.
4. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
5. Downgrade 1 level for serious risk of bias. Study demonstrates no blinding of outcome assessment.
6. Study did not explicitly specify criteria used for the classification of surgical site infections. Downgrade 1 level for serious indirectness.
7. Downgrade 2 levels for no measure of spread and non-significant results.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Outcomes at 6 months after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI (all surgeries) - RR <1 favours gentamicin collagen sponge										
2 Musella 2001, Yetim 2010	RCT	621	RR 0.14 (95% CI: 0.03, 0.76)	3 per 100 people	0 per 100 people (0, 2)	Serious[1]	Serious[2]	Not serious	Not serious	Low
SSI (Prosthetic repair of groin hernias) - RR <1 favours gentamicin collagen sponge										
1 Musella 2001	RCT	577	RR 0.16 (95% CI: 0.22, 1.33)	2 per 100 people	0 per 100 people (0, 3)	Serious[3]	Serious[4]	NA[5]	Very serious[6]	Very low
SSI (abdominoperineal resection) - RR <1 favours gentamicin collagen sponge										
1 Yetim 2010	RCT	44	RR 0.11 (95% CI: 0.01, 1.95)	18 per 100 people	2 per 100 people (0, 35)	Serious[7]	Serious[4]	NA[5]	Very serious[6]	Very low
Mean length of stay										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 Yetim 2010	RCT	44	MD: -4.68 (95% CI: -5.49, -3.87)	-	-	Serious[7]	Not serious	NA[5]	Not serious	Moderate

1. Downgrade 1 level for serious risk of bias. Greater than 33.3% of the weight in meta-analysis came from studies of moderate risk of bias due to unclear random sequence generation, allocation concealment and blinding of outcome assessment.
2. Greater than 33.3% of the weight in meta-analysis came from study partially direct study. Studies did not specify criteria used to classify surgical site infection. Downgrade 1 level for serious indirectness.
3. Downgrade 1 level for serious risk of bias. Study demonstrates unclear random sequence generation and allocation concealment.
4. Study did not specify criteria used to classify surgical site infection. Downgrade 1 level for serious indirectness.
5. Inconsistency not applicable
6. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
7. Downgrade 1 level for serious risk of bias. Study demonstrates unclear random sequence generation, allocation concealment and blinding of outcome assessment.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Outcomes at 1 year

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours gentamicin collagen sponge										
1 Collin 2013	RCT	91	RR not estimable due to no occurrence of event in either study arm.			Serious[1]	Not serious	NA[2]	Very serious[3]	Very low

1. Downgrade 1 level for serious risk of bias. Study demonstrates no blinding of outcome assessment.
2. Inconsistency not applicable
3. Unable to calculate effect size. Downgrade 2 levels for very serious imprecision.

Outcomes at 6-30 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI- RR <1 favours gentamicin collagen sponge										
1 Ozbalci 2014	RCT	50	RR not estimable due to no occurrence of event in either study arm.			Serious[1]	Serious[2]	NA[3]	Very serious[4]	Very low

1. Downgrade 1 level for serious risk of bias. Study demonstrates unclear random sequence generation, allocation concealment and blinding of outcome assessment.
2. Downgrade 1 level for partial indirectness. Study did not specify criteria used to classify surgical site infection.
3. Inconsistency not applicable
4. Unable to calculate effect size. Downgrade 2 levels for very serious imprecision.

Outcomes during postoperative period

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours gentamicin collagen sponge										
1 Rutten 1997	RCT	221	RR 0.30 (95% CI: 0.13, 0.73)	18 per 100 people	6 per 100 people (2, 13)	Serious[1]	Serious[2]	NA[3]	Not serious	Low

1. Downgrade 1 level for serious risk of bias. Study demonstrates unclear random sequence generation and blinding of outcome assessment.
2. Study did not specify follow up period. Downgrade 1 level for serious indirectness.
3. Inconsistency not applicable

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

G.10 Gentamicin collagen sponge vs collagen sponge alone (placebo)

Outcomes at 1 month after surgery

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SSI - RR <1 favours gentamicin collagen sponge										
2 Haase 2005, Schimmer 2012	RCT	800	RR 0.48 (95% CI: 0.25, 0.91)	7 per 100 people	3 per 100 people (2, 6)	Very serious[1]	Not serious	Not serious	Serious[2]	Very low
SSI (loop-ileostomy) - RR <1 favours gentamicin collagen sponge										
1 Haase 2005	RCT	80	RR 1.00 (95% CI: 0.27, 3.72)	10 per 100 people	10 per 100 people (3, 37)	Not serious	Not serious	NA[3]	Very serious[2]	Low
SSI (cardiac surgery) - RR <1 favours gentamicin collagen sponge										
1 Schimmer 2012	RCT	720	RR 0.39 (95% CI: 0.18, 0.83)	7 per 100 people	3 per 100 people (1, 5)	Very serious[4]	Not serious	NA[3]	Serious[5]	Very low
Superficial SSI - RR <1 favours gentamicin collagen sponge										
3 Haase 2005, Schimmer 2012, Pochammer 2015	RCT	993	RR 0.74 (95% CI: 0.42, 1.31)	5 per 100 people	4 per 100 people (2, 7)	Very Serious[6]	Not serious	Not serious	Very serious[2]	Very low
Sensitivity analysis (excluding studies at high risk of bias) Superficial SSI - RR <1 favours gentamicin collagen sponge										
2 Haase 2005, Pochammer 2015	RCT	273	RR: 0.79 (95% CI: 0.39, 1.63)	11 per 100 people	9 per 100 people (4,18)	Not serious	Not serious	Not serious	Very serious[2]	Low
Superficial SSI (loop-ileostomy) - RR <1 favours gentamicin collagen sponge										
1 Hasse 2005	RCT	80	RR 2.00 (95% CI: 0.39, 10.31)	5 per 100 people	10 per 100 people (2, 52)	Not serious	Not serious	NA[3]	Very serious[2]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Superficial SSI (cardiac surgery) - RR <1 favours gentamicin collagen sponge										
1 Schimmer 2012	RCT	720	RR 0.66 (95% CI: 0.26, 1.69)	3 per 100 people	2 per 100 people (1, 5)	Very serious[4]	Not serious	NA[3]	Very serious[2]	Very low
Superficial SSI (colorectal surgery) - RR <1 favours gentamicin collagen sponge										
1 Pochammer 2015	RCT	193	RR 0.61 (95% CI: 0.26, 1.40)	14 per 100 people	8 per 100 people (4, 19)	Not serious	Not serious	NA[3]	Very serious[2]	Low
Deep SSI - RR <1 favours gentamicin collagen sponge										
3 Haase 2005, Schimmer 2012, Pochammer 2015	RCT	993	RR 0.17 (95% CI: 0.04, 0.63)	3 per 100 people	1 per 100 people (0, 2)	Very serious[1]	Not serious	Not serious	Very serious[2]	Very low
Sensitivity analysis (excluding studies at high risk of bias) Deep SSI - RR <1 favours gentamicin collagen sponge										
Haase 2005, Pochammer 2015	RCT	272	RR 0.20 (95% CI: 0.01, 4.04)	15 per 1000 people**	3 per 1000 people (0,59)**	Not serious	Not serious	Not serious	Very serious[2]	Low
Deep SSI (loop-ileostomy) - RR <1 favours gentamicin collagen sponge										
1 Hasse 2005	RCT	80	RR 0.20 (95% CI: 0.01, 4.04)	5 per 100 people	1 per 100 people (0, 20)	Not serious	Not serious	NA[3]	Very serious[2]	Low
Deep SSI (cardiac surgery)										
1 Schimmer 2012	RCT	720	RR 0.16 (95%CI: 0.04, 0.70)	4 per 100 people	1 per 100 people (0, 2)	Very serious[4]	Not serious	NA[3]	Very serious[2]	Very low
Deep SSI (colorectal surgery) - RR <1 favours gentamicin collagen sponge										
1 Pochammer 2015	RCT	193	RR not estimable due to no occurrence of event in either study arm.			Not serious	Not serious	NA[3]	Very serious[6]	Low

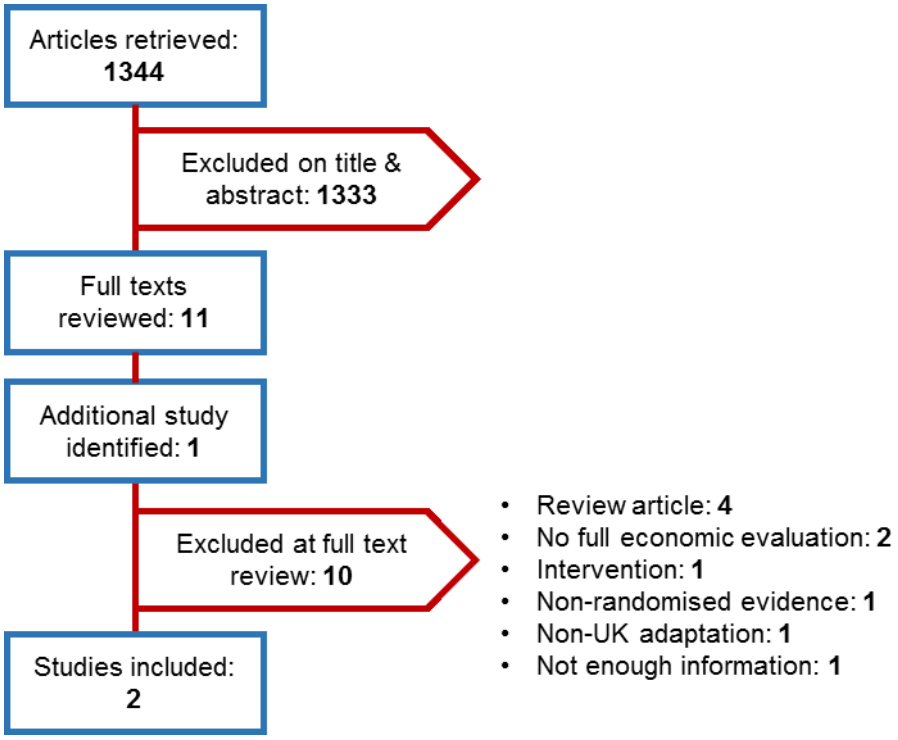
No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Length of stay										
1 Pochammer 2015	RCT	193	Difference in medians: 0.5 days (non- significant according to Kurskal-Wallis test)			Not serious	Not serious	NA[3]	Very serious[7]	Low

1. Downgrade 2 levels for very serious risk of bias. Greater than 33.3% of the weight in meta-analysis came from study of high risk of bias due to unclear random sequence generation, allocation concealment and blinding of outcome assessment. Furthermore, intention to treat analysis was not performed.
2. 95% confidence interval crosses both ends of a defined MID interval (0.8, 1.25). Downgrade 2 levels.
3. Inconsistency not applicable
4. Downgrade 2 levels for very serious risk of bias. Study demonstrates unclear random sequence generation, allocation concealment and blinding of outcome assessment. Furthermore, intention to treat analysis was not conducted.
5. 95% confidence interval crosses one end of a defined MID interval (0.8, 1.25). Downgrade 1 level.
6. Unable to calculate effect size. Downgrade 2 levels for very serious imprecision.
7. Downgrade 2 levels for no measure of spread and non-significant results.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

** Derived by taking the overall number of event/ total number of participants and multiplying by 1000

Appendix H – Economic evidence study selection



Appendix I – Economic evidence tables

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental (antibiotic vs. plain cement)			Conclusions	Uncertainty
			Cost	Effect (QALYs)	ICER		
Graves et al., (2016) Economic model comparing impregnated bone cement with plain bone cement, both alongside other infection control measures, in hip replacement patients. UK. **Partially applicable** [a, b] **Potentially serious limitations** [c, d, e]	Effects: Systematic literature review and meta-regression. Antibiotic bone cement deep SSI RR: 0.46 vs. plain bone cement (if conventional ventilation and no systemic antibiotics). Costs: Treatment costs from list prices, assuming an average of 30% confidential discount to NHS hospitals. Other costs from NHS reference costs 2012-13. Utilities: Utility weights from various sources, elicited by: AQoL, 15D or expert opinion.	Lifetime Markov model with 9 states. Discount rate: 3%. Nine strategies based on use of systemic antibiotics, type of theatre ventilation, and use of antibiotic bone cement. Treatment of SSI informed by linkage of 5 UK registry datasets. Mortality from UK life tables.	Analysis G1 [1] -£60 Analysis G2 [1] -£14 Analysis G3 [1] +£26	 +0.0011 +0.0006 +0.0001	 Dominant Dominant £333,215	'The conclusion from this research is that [systemic antibiotics, **antibiotic-impregnated cement** and conventional ventilation] is the best decision for NHS hospitals.'	PSA (1,000) model runs showed that antibiotic cement saves costs compared with plain cement with a likelihood of 96%, and generates more QALYs with a likelihood of 62%. PSA results were not presented for the other relevant head-to-head comparisons (i.e. where the variable intervention was only bone cement). However, systemic antibiotics, **antibiotic-impregnated cement** and conventional ventilation had the highest probability of being cost-effective overall (32%).

Key: 15D, 15 dimensions health-related quality of life instrument; AQoL, Assessment of Quality of Life; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; RR, relative risk.

Note: (1) Analysis G1: no systemic antibiotics, conventional theatre ventilation. Analysis G2: systemic antibiotics, conventional theatre ventilation. Analysis G3: systematic antibiotics, laminar airflow theatre ventilation.

Applicability: (a) Discount rate of 3% is used. (b) QALYs not derived using EQ-5D.

Quality: (c) PSA only conducted for 1 head-to-head comparison out of 3 that are relevant (and it does not really probability ICER < £20,000). (d) Costs subject to author assumption of 30% discount to list prices. (e) 5-year time horizon might miss differences in long-term life expectancy.

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental (antibiotic vs. plain cement)			Conclusions	Uncertainty
			Cost [1]	Effect (QALYs)	ICER		
Cummins et al., (2009) Economic model comparing impregnated bone cement with plain bone cement in hip arthroscopy patients. US. **Partially applicable** [a, b, c] **Potentially serious limitations** [d, e, f]	Effects: Cox regression based on 14-year Norwegian registry (m=22,170) data. Plain bone cement septic revision RR: 1.8 vs. antibiotic bone cement (aseptic revision: 1.3). Costs: Direct health care costs from various published sources. Price year: 2012. Utilities: Baseline utility value from patient TTO study. Revision decrements assumed to be 10% (aseptic) to 20% (septic), indirectly informed by SF-36 study.	Lifetime Markov model with 4 states. Discount rate: 3%. Cox regression attempted to control for potential confounders such as age, sex and the use of other infection control measures. Mortality from US life tables, except 0.23% operative death rate (from registry).	Analysis C1 [2] -$200 (-£141) Analysis C2 [2] +$200 (+£141)	+0.015 +0.009	Dominant $37,355 [3] (£15,612)	'The off-label use of antibiotic-impregnated bone cement for primary total hip arthroplasty with cement appears to be a cost-effective strategy if the patient population is young and the cost of the cement is relatively low.'	Sensitivity analysis showed the model is relatively sensitive to cost inputs and patient age. In Analysis C1, if the patient is 85, antibiotic bone cement must cost less than $500 (£351; -17% vs. base case) to obtain an ICER below a typical US threshold ($50,000; £35,127). In Analysis C2, including only septic revisions, its cost must be less than $350 (£246; -42% vs. base case).

Key: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; RR, relative risk; TTO, time trade-off.

Note: (1) Analysis C1: Treatment effect on aseptic and septic revisions included. Analysis C2: Treatment effect on septic revisions only. (2) Costs in 2012 US dollars converted to British pounds using HMRC exchange rate as at May 2018: £1 = $1.4234. (3) The reported ICER of $37,355 does not correspond with the incremental cost and QALY results. The ICER in UK currency has been directly recalculated using the reported incremental cost and QALY results.

Applicability: (a) Discount rate of 3% is used. (b) QALYs not derived using EQ-5D. (c) US setting.

Quality: (d) Utility decrements for revision procedure ultimately informed by author assumption. (e) No PSA. (f) Relative effects informed by non-randomised data.

Appendix J – Excluded studies

Clinical studies

Short Title	Title	
Abdullah (2017)	Topical vancomycin reduces surgical-site infections after craniotomy: a prospective, controlled study	• Conference abstract
Anagnostakos (2012)	Antibiotic-impregnated bone grafts in orthopaedic and trauma surgery: a systematic review of the literature	• Systematic review did not match review protocol
Anagnostakos (2017)	Therapeutic Use of Antibiotic-loaded Bone Cement in the Treatment of Hip and Knee Joint Infections	• Review article but not a systematic review
Andreas (2017)	Direct sternal administration of Vancomycin and Gentamicin during closure prevents wound infection	• Not a relevant study design Before and after study.
Bakhsheshian (2015)	The use of vancomycin powder in modern spine surgery: systematic review and meta-analysis of the clinical evidence	• Systematic review did not contain new relevant papers
Benaerts (1999)	Gentamicin beads in vascular surgery: long-term results of implantation	• Not a relevant study design Prospective observational study.
Bertazzoni (2004)	Release of gentamicin and vancomycin from temporary human hip spacers in two-stage revision of infected arthroplasty	• Study not relevant to RQ Study did not examine SSI.
Birgand (2013)	Does a gentamicin-impregnated collagen sponge reduce sternal wound infections in high-risk cardiac surgery patients?	• Not a relevant study design Before and after study.
Block (2005)	Reducing the risk of deep wound infection in primary joint arthroplasty with antibiotic bone cement	• Systematic review did not contain new relevant papers
Bozzetti (1975)	Topical ampicilin and local infectious complications in oncological surgery	• Study not reported in English
Chang (2013)	Gentamicin-collagen implants to reduce surgical site infection: systematic review and meta-analysis of randomized trials	• Systematic review did not contain new relevant papers
Chen (2014)	Antibiotic-loaded bone cement and periprosthetic joint infection	• Review article but not a systematic review
Chiang (2014)	Effectiveness of local vancomycin powder to decrease surgical site infections: a meta-analysis	• Systematic review did not contain new relevant papers

Short Title	Title	
Chiu (2001)	Cefuroxime-impregnated cement at primary total knee arthroplasty in diabetes mellitus. A prospective, randomised study	• Study not relevant to RQ Quasi randomised trial.
Chiu (2002)	Cefuroxime-impregnated cement in primary total knee arthroplasty: a prospective, randomized study of three hundred and forty knees	• Study not relevant to RQ Quasi randomised trial.
Creanor (2012)	Effectiveness of a gentamicin impregnated collagen sponge on reducing sternal wound infections following cardiac surgery: a meta-analysis of randomised controlled trials	• Systematic review did not contain new relevant papers
Culligan (2005)	A randomized trial that compared povidone iodine and chlorhexidine as antiseptics for vaginal hysterectomy	• Study does not contain any of the outcomes of interest
de Bruin (2010)	Local application of gentamicin collagen implants in the prophylaxis of surgical site infections following gastrointestinal surgery: a review of clinical experience	• Systematic review did not contain new relevant papers
de Bruin (2012)	Local application of gentamicin-containing collagen implant in the prophylaxis of surgical site infection following gastrointestinal surgery	• Systematic review did not contain new relevant papers
Desmond (2003)	Topical vancomycin applied on closure of the sternotomy wound does not prevent high levels of systemic vancomycin	• Study does not contain any of the outcomes of interest
Diefenbeck (2006)	Prophylaxis and treatment of implant-related infections by local application of antibiotics	• Review article but not a systematic review
Donovan (2018)	Sternal application of vancomycin greatly reduces the incidence of sternal wound complications in patients undergoing cardiosurgical procedures	• Conference abstract
Dunbar (2009)	Antibiotic bone cements: their use in routine primary total joint arthroplasty is justified	• Conference abstract
Eklund (2007)	Prevention of sternal wound infections with locally administered gentamicin	• Not a relevant study design. Summary of Eklund 2005.
Espehaug (1997)	Antibiotic prophylaxis in total hip arthroplasty. Review of 10,905 primary cemented total hip replacements reported to the Norwegian arthroplasty register, 1987 to 1995	• Not a relevant study design Retrospective cohort study.
Evaniew (2015)	Intrawound vancomycin to prevent infections after spine surgery: a systematic review and meta-analysis.	• Systematic review did not contain new relevant papers
Fleischman (2017)	Local Intra-wound Administration of Powdered Antibiotics in Orthopaedic Surgery	• Review article but not a systematic

Short Title	Title	
		review
Formanek (2014)	Gentamicin/collagen sponge use may reduce the risk of surgical site infections for patients undergoing cardiac operations: a meta-analysis	• Systematic review did not contain new relevant papers
Friberg (2007)	Incidence, microbiological findings, and clinical presentation of sternal wound infections after cardiac surgery with and without local gentamicin prophylaxis	• Study not relevant to RQ Study analysed the microbiological findings of sternal wound infections.
Friberg (2009)	Collagen-gentamicin implant for prevention of sternal wound infection; long-term follow-up of effectiveness	• Not a relevant study design Historical cohort.
Fry (2016)	Topical Antimicrobials and the Open Surgical Wound	• Review article but not a systematic review
Gaillard (1991)	Intra-operative antibiotic prophylaxis in neurosurgery. A prospective, randomized, controlled study on cefotiam	• Study not relevant to RQ Antibiotic was administered intravenously.
Ghobrial (2015)	Complications from the use of intrawound vancomycin in lumbar spinal surgery: a systematic review	• Systematic review did not match review protocol Review includes observational studies.
Gilmore (1977)	A study of the effect of povidone-iodine on wound healing	• Study not relevant to RQ Animal study.
Godbole (2012)	Use of gentamicin-collagen sponges in closure of sternal wounds in cardiothoracic surgery to reduce wound infections	• Systematic review did not contain new relevant papers
Godil (2013)	Comparative effectiveness and cost-benefit analysis of local application of vancomycin powder in posterior spinal fusion for spine trauma: clinical article	• Not a relevant study design Retrospective review
Gomez (2016)	Does antibiotic-loaded cement decrease the risk of aseptic failure in primary hip arthroplasty? A systematic review	• Study not reported in English
Gray (1983)	The role of prophylactic antibiotics in appendectomy using delayed primary closure	• Study not relevant to RQ Antibiotics used intravenously.
Guzman (1999)	Effectiveness of collagen-gentamicin implant for treatment of "dirty" abdominal wounds	• Comparator in study does not match that specified in protocol Intervention group received gentamicin sponge and comparator group received systemic gentamicin.

Short Title	Title	
Hendriks (2004)	Backgrounds of antibiotic-loaded bone cement and prosthesis-related infection	• Review article but not a systematic review
Hinarejos (2015)	Use of antibiotic-loaded cement in total knee arthroplasty	• Review article but not a systematic review
Hu (2016)	Efficacy and safety of local gentamicin collagen implanting for preventing SSI following colorectal surgery: A systematic review and meta-analysis	• Systematic review did not contain new relevant papers
Huiras (2012)	Local antimicrobial administration for prophylaxis of surgical site infections	• Review article but not a systematic review
Hussain (2012)	Local application of gentamicin-containing collagen implant in the prophylaxis and treatment of surgical site infection following vascular surgery	• Systematic review did not contain new relevant papers
Ibrahim (2002)	Comparison of local povidone-iodine antisepsis with parenteral antibacterial prophylaxis for prevention of infective complications of TURP: a prospective randomized controlled study	• Comparator in study does not match that specified in protocol Intervention compared to saline solution and intravenous antibiotics.
Jiranek (2006)	Antibiotic-loaded bone cement for infection prophylaxis in total joint replacement	• Review article but not a systematic review
Josefsson (1981)	Systemic antibiotics and gentamicin-containing bone cement in the prophylaxis of postoperative infections in total hip arthroplasty	• Comparator in study does not match that specified in protocol Systemic antibiotics used as comparator.
Josefsson (1990)	Prophylaxis with systemic antibiotics versus gentamicin bone cement in total hip arthroplasty. A five-year survey of 1688 hips	• Comparator in study does not match that specified in protocol Systemic antibiotics used as comparator.
Joseph (2003)	Use of antibiotic-impregnated cement in total joint arthroplasty	• Review article but not a systematic review
Kang (2015)	Intrasite vancomycin powder for the prevention of surgical site infection in spine surgery: a systematic literature review	• Systematic review did not contain new relevant papers
Kanj (2013)	Vancomycin prophylaxis of surgical site infection in clean orthopaedic surgery	• Systematic review did not contain new relevant papers

Short Title	Title	
Katarincic (2018)	Local Modalities for Preventing Surgical Site Infections: An Evidence-based Review	• Review article but not a systematic review
Khan (2014)	A meta-analysis of spinal surgical site infection and vancomycin powder	• Systematic review did not contain new relevant papers
Kleppel (2017)	Antibiotic bone cement's effect on infection rates in primary and revision total knee arthroplasties	• Systematic review did not match review protocol Included studies in which antibiotic bone cement was compared to intravenous antibiotics alone.
Knaepler (2012)	Local application of gentamicin-containing collagen implant in the prophylaxis and treatment of surgical site infection in orthopaedic surgery	• Systematic review did not contain new relevant papers
Kochanski (2017)	The effect of vancomycin powder on surgical site infections in deep brain stimulation surgery	• Conference abstract
Konstantelias (2016)	Gentamicin-Collagen Sponges for the Prevention of Surgical Site Infections: A Meta-Analysis of Randomized Controlled Trials	• Systematic review cross referenced to identify relevant studies.
Kowalewski (2015)	Gentamicin-collagen sponge reduces the risk of sternal wound infections after heart surgery: Meta-analysis	• Systematic review did not contain new relevant papers
Leyh (1999)	Adjuvant treatment of deep sternal wound infection with collagenous gentamycin	• Study does not contain any of the outcomes of interest
Lopez (2015)	Should we add vancomycin antibiotic powder to prevent post-operative infection in spine surgery? - First update	• Systematic review did not contain new relevant papers
Mallela (2017)	Topical Vancomycin Reduces Surgical-Site Infections After Craniotomy: A Prospective, Controlled Study	• Study not relevant to RQ Prospective cohort study.
Martinez-Moreno (2017)	Antibiotic-loaded Bone Cement as Prophylaxis in Total Joint Replacement	• Systematic review did not match review protocol
Mavros (2012)	Gentamicin collagen sponges for the prevention of sternal wound infection: a meta-analysis of randomized controlled trials	• Systematic review did not contain new relevant papers
Mavros (2013)	Antimicrobials as an adjunct to pilonidal disease surgery: a systematic review of the literature	• Systematic review did not match review protocol Review examined preoperative and postoperative antibiotic prophylaxis.

Short Title	Title	
Mishra (2014)	Role of topical application of gentamicin containing collagen implants in cardiac surgery	• Review article but not a systematic review
Morawiec (2012)	Local antibiotic therapy in rectal cancer surgery	• Study not relevant to RQ Prospective observational study.
Murphy (2017)	A review of the application of vancomycin powder to posterior spinal fusion wounds with a focus on side effects and infection. A prospective study	• Not a relevant study design Prospective cohort study.
Naunton (1980)	Prophylactic povidone iodine in minor wounds	• Does not contain a population of interest
Nelson (1993)	A comparison of gentamicin-impregnated polymethylmethacrylate bead implantation to conventional parenteral antibiotic therapy in infected total hip and knee arthroplasty	• Does not contain a population of interest
Nguyen (2016)	Local administration of gentamicin collagen sponge in surgical excision of sacrococcygeal pilonidal sinus disease: a systematic review and meta-analysis of the literature	• Systematic review did not contain new relevant papers
O'Toole (2017)	Local Antibiotic Therapy to Reduce Infection After Operative Treatment of Fractures at High Risk of Infection: A Multicenter, Randomized, Controlled Trial (VANCO Study)	• Not a relevant study design Study protocol.
Parvizi (2008)	Efficacy of antibiotic-impregnated cement in total hip replacement	• Systematic review did not contain new relevant papers
Periti (1998)	Antimicrobial prophylaxis in orthopaedic surgery: The role of teicoplanin	• Review article but not a systematic review
Pitt (1980)	Prophylactic antibiotics in vascular surgery. Topical, systemic, or both?	• Comparator in study does not match that specified in protocol Saline used as a comparator.
Raja (2012)	Local application of gentamicin-containing collagen implant in the prophylaxis and treatment of surgical site infection following cardiac surgery	• Systematic review did not contain new relevant papers
Randelli (2010)	Prophylactic use of antibiotic-loaded bone cement in primary total knee replacement	• Review article but not a systematic review
Rapetto (2016)	Gentamicin-Impregnated Collagen Sponge: Effectiveness in Preventing Sternal Wound Infection in High-Risk Cardiac Surgery	• Review article but not a systematic review

Short Title	Title	
Rice (2000)	Intraoperative topical tetracycline sclerotherapy following mastectomy: a prospective, randomized trial	• Comparator in study does not match that specified in protocol Saline used as a comparator.
Rodrigo-Perez (2016)	Use of cement with antibiotics as prophylaxis in hip replacement surgery: A literature review	• Study not reported in English
Rosen (1991)	Local gentamicin application for perineal wound healing following abdominoperineal rectum excision	• Study does not contain any of the outcomes of interest
Schiavone (2016)	Antibiotic-loaded bone cement reduces risk of infections in primary total knee arthroplasty? A systematic review	• Systematic review did not contain new relevant papers
Schimmer (2017)	Prevention of surgical site sternal infections in cardiac surgery: a two-centre prospective randomized controlled study	• Comparator in study does not match that specified in protocol Cyanoacrylate- based microbial skin sealant used as comparator.
Schultz (1983)	Septic complications after appendicectomy for perforated appendicitis. A controlled clinical trial metronidazole and topical ampicillin	• Comparator in study does not match that specified in protocol Study compared systemic metronidazole plus topic ampicillin to topical ampicillin alone.
Senthi (2011)	Infection in total hip replacement: Meta-analysis	• Study not relevant to RQ Study examined management of deep infection.
Shapiro (1986)	Randomized clinical trial of intra-operative antimicrobial prophylaxis of infection after neurosurgical procedures	• Study not relevant to RQ Intervention administered intravenously.
Simons (2001)	The role of topical antibiotic prophylaxis in patients undergoing contaminated head and neck surgery with flap reconstruction	• Study not relevant to RQ Study looked at intraoperative and postoperative use of intervention.
Stewart (2006)	Prevention of infection in arterial reconstruction	• Systematic review did not match review protocol Systematic review examined all pre-operative interventions.
Stewart (2007)	Prevention of infection in peripheral arterial reconstruction: a systematic review and meta-analysis	• Systematic review did not match review protocol Systematic review examined all pre-operative interventions.

Short Title	Title	
Van Hal (2017)	Vancomycin Powder Regimen for Prevention of Surgical Site Infection in Complex Spine Surgeries	• Not a relevant study design Before and after study.
Vander (1989)	Reduction of sternal infection by application of topical vancomycin	• Not a relevant study design Quasi randomised trial.
Vogel (1992)	Treatment of pilonidal sinus with excision and primary suture using a local, resorbable antibiotic carrier. Results of a prospective randomized study	• Study not reported in English
Voigt (2016)	Antibiotics and antiseptics for preventing infection in people receiving revision total hip and knee prostheses: A systematic review of randomized controlled trials	• Systematic review did not match review protocol
Wang (2013)	A systematic review and meta-analysis of antibiotic-impregnated bone cement use in primary total hip or knee arthroplasty	• Systematic review did not contain new relevant papers
Wang (2015)	Antibiotic bone cement cannot reduce deep infection after primary total knee arthroplasty	• Not a relevant study design Retrospective cohort study.
Woodard (2017)	Topical antibiotics for preventing surgical site infection in wounds healing by primary intention (Review)	• Not a relevant study design Commentary.
Xie (2017)	Effect of Intra-wound Vancomycin for Spinal Surgery: A Systematic Review and Meta-analysis	• Systematic review did not match review protocol Review included retrospective cohort studies and prospective case study.
Xiong (2014)	Topical intrawound application of vancomycin powder in addition to intravenous administration of antibiotics: A meta-analysis on the deep infection after spinal surgeries	• Systematic review did not contain new relevant papers
Yao (2018)	Prophylaxis of surgical site infection in adult spine surgery: A systematic review	• Systematic review examined a number of different strategies for prophylaxis of SSI.
Yetim (2010)	Effect of gentamicin-absorbed collagen in wound healing in pilonidal sinus surgery: a prospective randomized study	• Comparator in study does not match that specified in protocol Patients were randomised to receive gentamicin sponge or no sponge and postoperative antibiotics.
Yi (2014)	No decreased infection rate when using antibiotic-impregnated cement in primary total joint arthroplasty	• Systematic review did not contain new relevant papers

Short Title	Title	
Zhang (2013)	Extended antimicrobial prophylaxis after gastric cancer surgery: a systematic review and meta-analysis	• Systematic review did not match review protocol Study examined antibiotic prophylaxis before and after surgery.
Zheng (2014)	Control strategies to prevent total hip replacement-related infections: a systematic review and mixed treatment comparison	• Systematic review did not match review protocol Study examined mixed treatments (antibiotic- impregnated cement, antibiotic prophylaxis and laminar flow).
Zhou (2015)	Lack of efficacy of prophylactic application of antibiotic-loaded bone cement for prevention of infection in primary total knee arthroplasty: results of a meta-analysis	• Systematic review did not contain new relevant papers

Economic studies

Study	Full title	Primary reason for exclusion
Bradley 1999	Bradley M, Cullum N, Nelson EA, et al. (1999). Systematic review of wound care management: (2) dressings and topical agents used in the healing of chronic wounds. *Health Technol Assess,* 3 (17).	Review article, no additional CUAs
Etchells 2012	Etchells E, Koo M, Daneman N, et al. (2012). Comparative economic analyses of patient safety improvement strategies in acute care: a systematic review. *BMJ Qual Saf,* 21: 448-56.	Review article, no additional CUAs
Gillespie 2017	Gillespie BM, Chaboyer W, Erichsen-Andersson A, et al. (2017). Economic case for intraoperative interventions to prevent surgical-site infection. *Br J Surg,* 104: e55-64.	Review article, no additional CUAs
Hatch 2017	Hatch MD, Daniels SD, Glerum KM, Higgins LD (2017). The cost effectiveness of vancomycin for preventing infections after shoulder arthroplasty: a break-even analysis. *J Shoulder Elbow Surg,* 26 (3): 472-7.	Not a full economic evaluation
Hernandez-Vaquero 2013	Hernández-Vaquero D, Fernández-Fairen M, Torres A, et al. (2017). Treatment of periprosthetic infections: an economic analysis. *Scientific World Journal,* 11.	Review article, no additional CUAs
Mallela 2017	Mallela AN, Abdullah KG, Brandon C, et al. (2017). Topical vancomycin reduces surgical-site infections after craniotomy: a prospective, controlled study. *Neurosurgery,* ePub ahead of print.	Based on non-randomised evidence
Merollini 2013	Merollini KMD, Crawford RW, Whitehouse SL, Graves N. (2013). Surgical site infection prevention following total hip arthroplasty in Australia: a cost-effectiveness analysis. *Am J Inf Control,* 41: 803-9.	Same model as included study (Graves et al., 2016), adapted to non-UK setting.
Pan & Dendukuri 2010	Pan I & Dendukuri N (2010). Efficacy and cost-effectiveness of a gentamicin-loaded collagen sponge as an adjuvant antibiotic prophylaxis for colorectal surgery. *Technology Assessment Unit Report 41.*	Insufficient information provided
Schwebel 2012	Schwebel C, Lucet J-C, Vesin A, et al. (2012). Economic evaluation of chlorhexidine-impregnated sponges for preventing catherer-related infections in	Intervention (post-operative)

Study	Full title	Primary reason for exclusion
	critically ill adults in the Dressing Study. *Crit Care Med,* 40 (1): 11-7.	
Trentinaglia 2018	Trentinaglia MT, van der Straeten C, Morelli I, et al. (2018). Economic evaluation of antibacterial coatings on healthcare costs in first year following total joint arthroplasty. *J Arthroplasty,* Epub ahead of print.	Not a full economic evaluation

Appendix K – Research recommendations

1. Is the application of antiseptics and antibiotics in the operative field before wound closure, clinically and cost effective in reducing surgical site infection rates?

30 RCTs were identified in this review which examined the clinical effectiveness of different topical antiseptics and antibiotics. This evidence ranged from moderate to very low quality and examined a number of different interventions including antibiotic loaded bone cement. Old and out-dated evidence suggested that interventions such as ampicillin, cephaloridine (which is no longer available on the market) and topical povidone iodine reduced the incidence of SSI. More recent data mainly suggests that gentamicin collagen implant are effective in reducing SSI in cardiac surgery and hidradenitis supperativa surgery.

As new interventions are being introduced into practice, further research is required, using a robust study design, to further explore the role of antibiotics and antiseptics in the reduction of SSI when applied intraoperatively. These studies should be adequately powered and should also further explore interventions such as antibiotic impregnated implants and antibiotic loaded bone cement. Further research should be based in the UK and take into account different surgical procedures. Research in this area is essential to inform future updates of key recommendations in this guidance which in turn can help improve patient outcomes.

PICO	**Population:**
	People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery)
	
	Interventions:
	Different antibiotics and antiseptics applied to the operative field (including antibiotic impregnated implants and antibiotic loaded bone cement)
	
	Comparator:
	• Placebo
	• No treatment
	• Interventions compared to each other
	
	Outcomes:
	• Surgical site infection (superficial, deep and organ/space SSI), including SSIs up to 30 days and 1 year, defined using appropriate criteria such as CDC SSI criteria.
	• Mortality post-surgery
	• Length of hospital stay
	• Postoperative antibiotic use.
	• Infectious complications such as septicaemia or septic shock
	• Adverse events:
	  ○ Antimicrobial resistance
	  ○ Organ toxicity
	  ○ Anaphylaxis
	• Resource implication

Current evidence base	Overall, 30 studies identified, 10 of which were conducted before the 1990s.
Study design	Randomised controlled trial

Other comments	These studies should take into account different surgery procedures and should be conducted within the UK with an adequate sample size.

Appendix L – References

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