Health economic model report

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Peter Jenks generously provided audit data for a hospital in Plymouth, enabling us to carry out a detailed analysis of each of the antiseptic skin agents used in the Jenks study.

All errors that remain are the responsibility of the developers and the guideline committee.

Economic modelling was prioritised for 2 review questions for this 2018 update to the *Surgical site infections: prevention and treatment* guideline. These are detailed below and in the economic plan. This report presents the methods and result of these original analyses.

Details of the systematic literature reviews to identify published economic evaluations are provided in each evidence review.

HE.1 RQ1

HE.1.1 Introduction

HE.1.1.1 Decision problem

Table HE01: Review questions

Does the use of nasal decontamination to eliminate *Staphylococcus aureus* (alone or in combination with other interventions) affect the rate of surgical site infection?

The effectiveness of nasal decontamination to eliminate *Staphylococcus aureus* was identified as an area of priority for new economic analysis. The original guideline (CG74), published in 2008, recommended against the use of nasal decontamination strategies, as their effectiveness and cost effectiveness were characterised by significant uncertainty. New clinical trials have since been published, and should be considered in an updated clinical and economic evaluation. Furthermore, the guideline development committee advised that nasal decontamination remains an area of uncertainty in current NHS practice and, due to the volume of surgical procedures conducted, a recommendation that seeks to standardise practice could have important resource implications.

Table HE02: PICO

Population	People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery)
Intervention	The usage and timing of the following treatments in combination with or without a chlorhexidine body wash or glycopeptide prophylaxis: • Intranasal mupirocin • Nasal Povidone-Iodine solution • Chlorhexidine nasal gel • Chlorhexidine and neomycin cream (Naseptin) Octenisan nasal gel
Comparator	• Placebo • No decontamination Different nasal decontamination procedures
Outcomes	• Surgical site infections (superficial, deep and organ/space SSI) including MRSA and MSSA SSI defined using appropriate criteria such as CDC SSI criteria. (Including SSIs up to 30 days and 1 year). • Other types of nosocomial infections • Mortality post-surgery • Length of hospital stay • Postoperative antibiotic use • Hospital readmission • Infectious complications such as septicaemia or septic shock • Adverse events: Antimicrobial resistance

The only nasal decontamination intervention included in the model is **mupirocin nasal ointment.** This intervention was the subject of the vast majority of clinical trials. When we focused on trials that reported the incidence of *S. aureus* SSIs in carriers of *S. aureus,* it was the only intervention with randomised comparative effectiveness evidence. The first strategy is therefore **universal mupirocin,** that is, mupirocin used for the nasal decontamination of all surgical patients in addition to routine infection control procedures. We compared this with a **standard care** strategy, which represents routine procedures – such as preoperative chlorhexidine washing – without nasal decontamination. A third strategy is to use **mupirocin only in carriers.** This strategy necessarily includes a preoperative screening component. Although the present decision problem is not focused on the effectiveness or cost effectiveness of screening programmes or methods, the expert guideline committee advised that the use of nasal decontamination may be predicated on the results of a screening test to identify carriers of *S. aureus.* Due to this, and based on the NICE Guide to methods of technology appraisal (2013), it becomes necessary to capture differences in the costs and benefits associated with screening.

To summarise, the 3 strategies included in this model are:

- Universal use of mupirocin nasal ointment (plus standard care)
- Use mupirocin nasal ointment only in carriers of *S. aureus* (plus standard care for all)
- Do not use mupirocin nasal ointment (standard care only)

HE.1.1.2 Nasal decontamination

HE.1.1.3 General

We built a cost–utility model to evaluate the cost effectiveness of alternative nasal *S. aureus* decontamination strategies prior to surgery. The model is a decision tree, designed to capture the short-term decision about whether to use nasal decontamination or not prior to surgery, with a similar structure to the 2008 CG74 model. At model entry a patient has just

undergone a surgical procedure, from which they are subject to a risk of SSI and mortality. For the purpose of this decision problem, the model focuses on SSIs caused by *S. aureus.* After the perioperative period, the model applies age-related life expectancy to surviving patients. In this way, the full impact of differences in SSI-related mortality on health gains are captured.

The model takes a patient perspective for outcomes and an NHS and PSS perspective for costs, in line with Developing NICE guidelines (NICE 2014). The key health economic outcomes, used to determine cost effectiveness, are incremental costs and quality-adjusted life years (QALYs), and the resulting incremental cost-effectiveness ratio (ICER). As per Developing NICE guidelines (NICE 2014), future QALYs experienced during the post-surgery life expectancy calculations are discounted at a rate of 3.5% per year. For costs, discounting is not relevant as all costs are incurred within the first year. This reflects societal time preference; health benefits accrued next year are less important than health benefits accrued today.

HE.1.1.4 Identifying sources of parameters

Relative effectiveness inputs have been derived from the randomised trials in this area, identified by the clinical systematic literature review. When searching for quality of life, resource use and cost parameters, searches were conducted in specific databases designed for this purpose: the CEA (Cost-Effectiveness Analysis) Registry and the NHS Economic Evaluation Database (NHS EED). We also referred to economic modelling conducted in the original guideline (2008), or asked the 2018 expert guideline development committee, to identify model parameters and data sources, where required.

Selecting parameters

Our overriding selection criteria were as follows:

- The selected studies should report outcomes that correspond as closely as possible to the health states and events simulated in the model.
- The selected studies should report a population that closely matches the target population (ideally, they should be drawn from the UK and should be relevant to the population specified in the decision problem).
- All other things being equal, more powerful studies (based on sample size and/or number of events) were preferred.
- Where there was no reason to discriminate between multiple possible sources for a given parameter, we gave consideration to quantitative synthesis (meta-analysis), to provide a single summary estimate.

HE.1.2 Methods

HE.1.2.1 Model structure

As described above, the model takes a decision tree structure. Patients enter the model at the point of undergoing a surgical procedure, which carries a risk of contracting an *S. aureus* SSI for 30 days. The risk of SSI is dependent on whether the person is a carrier of *S. aureus* or a non-carrier, and whether nasal decontamination was performed prior to surgery (which may be directly determined by the results of preoperative screening). Patients also face an increased risk of mortality during this period, which may be further increased by the presence of an SSI. At the end of 30 days, patients will go on to experience residual recovery back to their baseline quality of life (see Section HE.1.2.6), and then surviving individuals will experience the remainder of their life-expectancy and general, age-related quality of life.

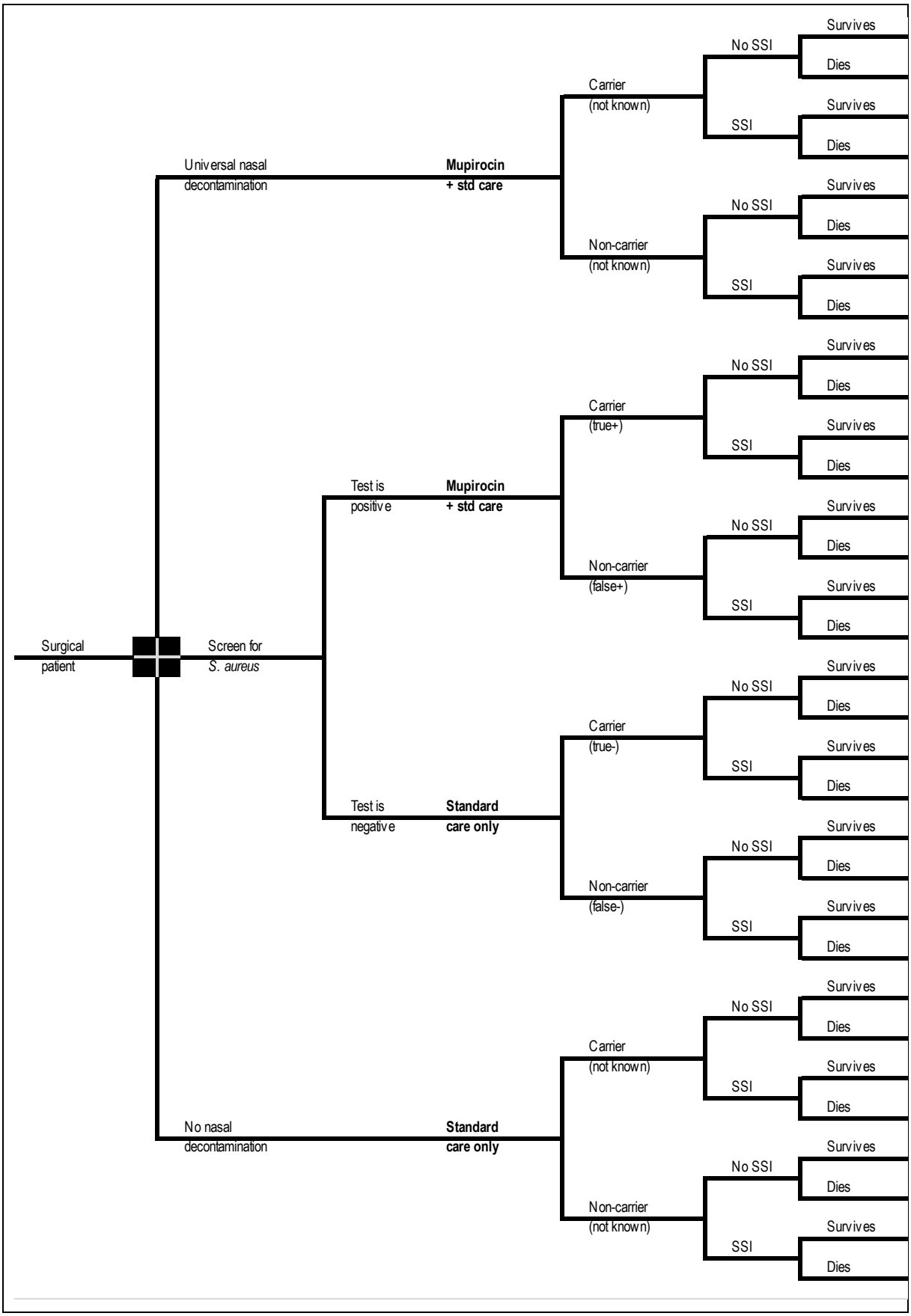


Figure HE01: Structure of nasal decontamination model

HE.1.2.2 Baseline parameters

Relevant baseline model parameters are:

- age
- sex
- type of surgery
- baseline incidence of SSI
- proportion of SSIs caused by *S. aureus*
- prevalence of nasal *S. aureus* carriage

HE.1.2.2.1 Demographics

In our base-case analysis, the age and sex of the surgical patient cohort are informed by PHE SSI surveillance service data, which reflects open incisional procedures (so may not perfectly represent the full population of surgical patients). The mean age across all surgery types is 70 years, and 42% of surgical procedures were conducted on male patients. The model can consider different surgical subgroups, for which the PHE data provide specific age and sex data (Table HE03).

Table HE03: Age and sex of surgical patients by surgery type (PHE, 2017)

Surgery type	Mean age (SE)	Proportion male (SE)
Abdominal hysterectomy	50.8 (0.52)	0% (0)
Bile duct, liver or pancreas	58.6 (0.80)	41.4% (0.022)
Breast	57.7 (0.26)	2.2% (0.002)
Cholecystectomy	51.4 (1.10)	63.0% (0.008)
CABG	68.3 (0.13)	26.2% (0.024)
Cardiac (non-CABG)	63.2 (0.32)	81.9% (0.005)
Cranial	56.3 (0.44)	54.8% (0.011)
Gastric	59.3 (0.78)	48.5% (0.024)
Hip prosthesis	70.3 (0.06)	39.6% (0.002)
Knee prosthesis	70.0 (0.05)	42.8% (0.002)
Large bowel	67.6 (0.23)	51.9% (0.008)
Limb amputation	67.6 (0.88)	72.1% (0.024)
Reduction of long bone fracture	60.5 (0.59)	39.4% (0.010)
Repair of neck of femur	84.3 (0.06)	30.5% (0.003)
Small bowel	59.2 (0.60)	53.4% (0.015)
Spinal	53.6 (0.26)	47.0% (0.006)
Vascular	73.0 (0.29)	71.0% (0.013)
All surgery (weighted average)	**70.0**	**42.0%**

Key: CABG, coronary artery bypass graft; SE, standard error.

HE.1.2.2.2 SSI incidence

Two sources were identified to inform baseline SSI incidence: a study of over 14,000 surgical episodes conducted in a hospital in England (Jenks et al., 2014) and data from the PHE SSI surveillance service (PHE, 2017), comprising 140,000 surgical episodes in the NHS. Both provide the overall SSI rate – including those not caused by *S. aureus* – for a number of different types of surgery. Being a national source comprising data from 142 NHS trusts (201 hospitals), and a larger dataset, our strong bias (see HE.1.1.4) would be to prefer the PHE data as more likely to be representative of current NHS outcomes. However, the guideline

committee advised that the PHE SSI surveillance service data are likely to produce conservative estimates of SSI incidence than are observed in practice. There are a number of reasons for this, including that data submission to the service is mostly voluntary, and it is, by and large, not informed by systematic surveillance that will identify SSIs arising in the community after discharge. In contrast, the single-centre study was extremely inclusive in estimating *all* SSIs at the centre. Unsurprisingly, then, the SSI rates reported by Jenks et al. are notably higher than those from the PHE SSI surveillance service, except in cranial and spinal surgery (see Table HE04). The committee was keen to understand the implications of adopting either dataset for the baseline estimate of SSI in the model. For the base case, it preferred the Jenks et al. study, as it agreed that under-reporting of SSIs is a greater danger than over-reporting, and committee members agreed that the rates in the published study were more representative of their own experiences in practice. The PHE SSI surveillance service data were used in sensitivity analysis.

Since our treatment of interest seeks to decontaminate the nasal passage of *S. aureus,* we are interested in the rate of SSIs caused by *S. aureus.* We therefore required the proportion of all SSIs that were caused by *S. aureus*, rather than some other cause. The single-centre study reports that 33% of SSIs are caused by *S. aureus,* compared with 11% in the PHE SSI surveillance service data (although this estimate relates to inpatient-detected SSIs only; for inpatient and readmission-detected SSIs, the proportion is 20%).

We present 2 separate analyses using each source – the single-centre study and the PHE SSI surveillance service – to inform baseline SSI rates. Given that nasal decontamination is not currently recommended for NHS practice, these baseline rates are assumed to reflect the SSI rate associated with standard care.

Table HE04: Baseline SSI incidence – unknown *S. aureus* carriage status

Surgery type	Jenks et al., 2014	PHE, 2017
All-cause SSI		
Abdominal hysterectomy	3.5% (0.009)	1.4% (0.002)
Bile duct, liver or pancreas	9.5% (0.020)	6.0% (0.005)
Breast	4.8% (0.007)	0.9% (0.001)
Cholecystectomy	13.0% (0.050)	2.7% (0.004)
CABG	10.8% (0.008)	3.8% (0.001)
Cardiac (non-CABG)	10.8% (0.008)	1.3% (0.001)
Cranial	1.0% (0.003)	1.6% (0.001)
Gastric	3.9% (0.013)	2.2% (0.004)
Hip prosthesis	1.6% (0.004)	0.6% (<0.001)
Knee prosthesis	3.2% (0.006)	0.6% (<0.001)
Large bowel	12.8% (0.013)	9.2% (0.002)
Limb amputation	4.5% (0.012)	2.8% (0.004)
Reduction of long bone fracture	2.1% (0.004)	1.0% (0.001)
Repair of neck of femur	2.3% (0.006)	1.1% (<0.001)
Small bowel	9.3% (0.018)	6.6% (0.004)
Spinal	1.0% (0.002)	1.4% (0.001)
Vascular	7.0% (0.013)	2.7% (0.002)
All surgery	5.1% (0.002)	1.3% (<0.001)
SSI caused by *S. aureus*		
Proportion caused by *S. aureus*	33.2% (0.004)	11.0% (0.003)

Key: CABG, coronary artery bypass graft; SE, standard error.

HE.1.2.2.3 Nasal carriage of *S. aureus*

The baseline incidence of SSI, and the effectiveness of nasal decontamination, are likely to be influenced by whether or not the individual is a nasal carrier of *S. aureus* in the first place. The prevalence of nasal carriage of *S. aureus* in the general UK surgical population is informed by a large cross-sectional study across 9 European countries, including 3,156 UK observations (den Heijer et al., 2013), which reports a UK prevalence of 25%. Given that one of our model strategies includes a screening component, which aims to identify carriers, it is important to reflect differences in baseline SSI rates and treatment effects between carriers and non-carriers.

We sought to adjust the baseline SSI rates shown above to reflect the carrier status of the individual. To do this, we used data from those trials identified in the clinical evidence search that reported the incidence of *S. aureus* SSIs on a control arm for both confirmed carriers and non-carriers. In practice, no trials reported outcomes in non-carriers, but 2 did report outcomes for both carriers and the whole cohort. As any trial cohort is composed entirely of carriers and non-carriers, this information allowed us to identify incidence of *S. aureus* SSI in both carriers and non-carriers on trial control arms. One of these trials also reported the incidence of *any cause* SSI for both carriers and the whole cohort.

We used the *S. aureus* SSI data to calculate odds ratios to characterise the impact of carrier status on the baseline incidence of SSI. The first step was to take the baseline any cause SSI incidence rates, from general populations of unknown carrier status (Table HE04), and reduce them to reflect the incidence of *S. aureus* SSI. This is based on the proportion of all SSIs caused by *S. aureus:* 33% based on the single-centre study, 11% based on the PHE data.

We then use odds ratios to estimate the effect of carrier status on incidence of *S. aureus* SSI, derived from 2 trials, to estimate the equivalent rates in carriers and non-carriers. The trials for this analysis, both comparing mupirocin with no nasal decontamination, were Kalmeijer et al. (2002) and Perl et al. (2002). In total, they recorded 54 *S. aureus* SSIs in 2,193 surgical patients. They recorded 31 *S. aureus* SSIs in 534 known carriers. We can therefore calculate that 23 *S. aureus* SSIs occurred in 1,659 non-carriers. From these data, the pooled odds ratios related to carrier status are as follows:

- Carrier vs. whole population: **2.44** (95%CI: 1.82–3.28)
- Carrier vs. non-carrier: **4.38** (95%CI: 2.85–6.73).

These odds ratios are applied to the values of baseline *S. aureus* SSI incidence. The resulting estimates for baseline incidence in carriers and non-carriers, for different types of surgery, are presented in Table HE05.

Alternative scenario: any cause SSI data

An alternative approach was identified that uses the incidence *any cause* SSI for both carriers and the whole cohort, from the 1 trial that reports these data (Perl et al., 2002). Here, we first take the baseline any cause SSI incidence rates again (Table HE04), and then use odds ratios to estimate the effect of carrier status on incidence of *any cause* SSI, derived from 1 trial, to estimate the equivalent rates in carriers and non-carriers. Perl et al. (2002) is the only trial that provides sufficient data for this. The study recorded 164 *any cause* SSIs in 1,931 surgical patients. They recorded 52 in 447 known carriers of *S. aureus*. We can therefore calculate that 112 *any cause* SSIs occurred in 1,484 non-carriers. From these data, the odds ratios related to carrier status are as follows:

- Carrier vs. whole population: **1.42** (95%CI: 1.15–1.75)
- Carrier vs. non-carrier: **1.61** (95%CI: 1.20–2.17).

These odds ratios are applied to the values of baseline *any cause* SSI incidence, providing separate estimates for carriers and non-carriers. We then reduce these values to reflect the proportion of all SSIs caused by *S.* aureus in carriers and non-carriers, also obtained from the Perl et al. trial: 50% in carriers (26/52) and 18% in non-carriers (20/112).

The resulting estimates for baseline incidence of *S. aureus* SSIs in carriers and non-carriers, for different types of surgery, are presented in Table HE05.

Table HE05: Baseline SSI incidence by *S. aureus* carrier status

Surgery type	Base case approach			Scenario analysis			
	S. aureus: Overall	*S. aureus: Carriers*	*S. aureus: Non-carriers*	*Any cause: Carriers*	*Any cause: Non-carriers*	*S. aureus: Carriers*	*S. aureus: Non-carriers*
Abdominal hysterectomy	1.2%	2.8%	0.6%	4.9%	3.1%	2.4%	0.5%
Bile duct, liver or pancreas	3.1%	7.3%	1.8%	12.9%	8.4%	6.5%	1.5%
Breast	1.6%	3.8%	0.9%	6.7%	4.3%	3.4%	0.8%
Cholecystectomy	4.3%	10.0%	2.5%	17.5%	11.7%	8.8%	2.1%
CABG	3.6%	8.3%	2.0%	14.6%	9.6%	7.3%	1.7%
Cardiac (non-CABG)	3.6%	8.3%	2.0%	14.6%	9.6%	7.3%	1.7%
Cranial	0.3%	0.8%	0.2%	1.4%	0.9%	0.7%	0.2%
Gastric	1.3%	3.1%	0.7%	5.5%	3.5%	2.8%	0.6%
Hip prosthesis	0.5%	1.3%	0.3%	2.3%	1.4%	1.2%	0.3%
Knee prosthesis	1.1%	2.6%	0.6%	4.5%	2.8%	2.2%	0.5%
Large bowel	4.2%	9.8%	2.4%	17.2%	11.4%	8.6%	2.0%
Limb amputation	1.5%	3.5%	0.8%	6.2%	4.0%	3.1%	0.7%
Reduction of long bone fracture	0.7%	1.7%	0.4%	2.9%	1.8%	1.5%	0.3%
Repair of neck of femur	0.8%	1.9%	0.4%	3.3%	2.1%	1.6%	0.4%
Small bowel	3.1%	7.2%	1.7%	12.7%	8.2%	6.3%	1.5%
Spinal	0.3%	0.8%	0.2%	1.4%	0.9%	0.7%	0.2%
Vascular	2.3%	5.5%	1.3%	9.6%	6.2%	4.8%	1.1%
All surgery	1.7%	4.1%	1.0%	7.1%	4.5%	3.6%	0.8%

Both approaches produce comparable baseline *S. aureus* SSI rates. The first method adjusts baseline incidence for *S. aureus* causation as the first step. The second method adjusts baseline incidence for *S. aureus* causation as the last step, applying differential *S. aureus* causality to carriers and non-carriers; however it uses less data to estimate its carrier status odds ratios, from 1 trial instead of 2. We have no preference between the 2 methodologically, and therefore use the first in our base-case analysis as it is based on more data.

HE.1.2.3 Treatment effects

Randomised controlled trials identified in the clinical evidence review were used as the source of relative effectiveness data. Trials either reported outcomes in *S. aureus* carriers, or general cohorts composed of some carriers and some non-carriers, or both. It was necessary for us to consider the treatment effect in *S. aureus* carriers specifically, because the inclusion of screening in the economic model provides information about a person's carrier status,

informing the subsequent treatment decision. Only those screened positive will receive treatment. It is plausible to expect nasal decontamination to have a bigger impact of the risk of *S. aureus* infection in carriers than non-carriers, and people who have screened positive for *S. aureus* will, on average, be more likely to actually carry *S. aureus* than a member of a general trial cohort. It would therefore be inappropriate to apply a treatment effect obtained from a general cohort to these patients.

We therefore focused on carrier trials that reported *S. aureus* SSI as an outcome, because: (1) we would expect decontamination of *S. aureus* to have a treatment effect only on people in whom *S. aureus* is actually present; and (2), nasal decontamination of *S. aureus* implicitly targets a reduction in the risk of SSI caused by *S. aureus.* This led to 5 mupirocin trials being meta-analysed, listed in Table HE06, comparing mupirocin with either placebo or no nasal decontamination. These are the data from section F.6 in Evidence review A (although, for computational purposes, we consider the relative effects on an odds ratio scale rather than the relative risks that are presented in the evidence review).

Fixed-effect and random-effects meta-analyses were conducted, with little variation in the resulting *S. aureus* SSI odds ratios for mupirocin compared with no mupirocin (Table HE07). All but 1 of the 5 trials (Kalmeijer et al., 2002) reported that chlorhexidine body wash was used as standard infection control treatment. The guideline committee advised that Mohs surgery – the setting for Tai et al. (2013) – is highly specialised, and potentially unrepresentative of general surgical practice. We therefore conducted sensitivity analyses in which the data from these 2 trials were removed from the meta-analysis. This has only a small bearing on the odds ratio point estimate, but increases uncertainty around the estimate due to reducing the pooled sample size (Table HE07).

Table HE06: Trials used to inform relative effectiveness of mupirocin vs. no mupirocin – *S. aureus* SSI – carriers of *S. aureus*

Study short name	Comparator	Type of surgery
Bode et al. (2010)	Placebo	Cardiothoracic Gastrointestinal General Orthopaedic Vascular
Kalmeijer et al. (2002)	Placebo	Orthopaedic
Konvalinka et al. (2006)	Placebo	Cardiac
Perl et al. (2002)	Placebo	Cardiothoracic General Gynaecological Neurological
Tai et al. (2013)	No nasal decontamination	Mohs

Table HE07: Relative effectiveness of mupirocin vs. no mupirocin – *S. aureus* SSI – carriers of *S. aureus*

Scenario	Odds ratio – FE (95%CI)	Odds ratio – RE (95%CI)
Base case: all 5 trials included	**0.47** (0.31–0.70)	**0.47** (0.30–0.73)
Exclude Kalmeijer et al. (2002) *No mention of chlorhexidine body wash*	**0.47** (0.31–0.75)	**0.48** (0.28–0.83)
Exclude Tai et al. (2013) *Highly specialised Mohs surgery*	**0.49** (0.32–0.75)	**0.50** (0.29–0.87)
Exclude both Kalmeijer and Tai trials	**0.50** (0.32–0.78)	**0.53** (0.26–1.06)
Key: CI, confidence interval; FE, fixed effects; RE, random effects.		

The odds ratios in Table HE07 are applied in the economic model to **treated carriers,** as follows:

- On the universal mupirocin arm, where all the patients receive mupirocin, all carriers (25% of the cohort) will experience a reduction in their risk of *S. aureus* SSI. The baseline risk (see Table HE05) is reduced according to the odds ratio in Table HE07. Non-carriers are assumed to experience no treatment effect; their risk of *S. aureus* SSI remains at the baseline value (see Table HE05).
- On the 'screen-and-treat' arm, patients who are screened positive for *S. aureus* will receive mupirocin. Only correctly-identified patients (true positives) will receive the treatment effect odds ratio. Non-carriers who were incorrectly identified as carriers, and subsequently treated, will experience no reduction in their baseline risk of *S. aureus* SSI, as there is no *S. aureus* present in these patients. Patients who are screened negative for *S. aureus* will not receive mupirocin, and will therefore experience no treatment effect; however, some of them will actually be carriers of *S. aureus* (false negatives), subject to a higher baseline risk of infection (Table HE05).
- On the no nasal decontamination arm, no patients receive mupirocin. All carriers (25% of the cohort) will be subject to the higher, carrier baseline risk of *S. aureus* SSI. Non-carriers will be subject to the lower, non-carrier baseline risk.

HE.1.2.4 Mortality

HE.1.2.4.1 SSI mortality

The economic model developed for the initial CG74 publication incorporated a higher risk of death in people who experienced SSI: 6.6%, compared with 2.6% in people who do not experience an SSI. This was derived from a Nosocomial Infection National Surveillance Service report on over 67,000 surgical procedures in England (Coello et al., 2005). However, more recent evidence, summarised in a review by Badia et al. (2017), presents a mixed picture regarding whether SSI causes excess mortality. The present guideline committee was of the opinion that the presence of an SSI must, logically, increase a person's risk of death, but recognised that this effect may be difficult to detect in a study, due to the low incidence of SSI generally and low risk of mortality. The committee still felt that it was important to attempt to quantify excess mortality associated with SSI.

To implement this into the model, we pooled the mortality odds ratios for 8 types of surgery, for SSI relative to no SSI, from Coello et al. (2005). This resulted in an overall odds ratio of 1.45; that is, the odds of death are 45% higher if the person has an SSI. This relative effect was assumed to obtain across all types of surgery, an assumption that is supported by Coello et al.'s data – the odds ratios are consistent with a null hypothesis of no difference between different surgery types (p=0.38; I^2=7%).

We then took baseline mortality rates for each of the model's 17 surgery types from the PHE (2017) dataset. Mortality rates were not reported in the Jenks et al. hospital study. These baseline mortality rates are average values for the PHE cohort, some of whom will have experienced an SSI, the rest of whom will not have. Next, we took the surgery-specific baseline probability of SSI from the PHE data (see Table HE04); this dataset was selected to be consistent with the baseline mortality rates. We therefore had: the overall mortality rate; the proportion of the cohort who had an SSI; and an odds ratio for mortality with SSI versus without SSI.

With these 3 pieces of information, it is possible to estimate separate mortality odds without SSI and with SSI, using the following formula:

$$MortalityOdds_{All} = probNoSSI * MortalityOdds_{NoSSI} + probSSI * MortalityOdds_{SSI}$$

Which can be rearranged as follows:

$$MortalityOdds_{NoSSI} = \frac{MortalityOdds_{All}}{[(1 - probSSI) + (probSSI * OR_{SSI})]}$$

Then:

$$MortalityOdds_{SSI} = MortalityOdds_{NoSSI} * OR_{SSI}$$

The mortality odds can then be converted into probabilities. In the base-case, all surgery population, the average, overall mortality rate from the PHE data is 1.31%. Using the PHE SSI rate, 1.3% of the overall population experienced SSI. With an SSI mortality odds ratio of 1.45, we can use the formulae above to estimate that the mortality rate without SSI is 1.30%, lower than the average value, and the rate with SSI is 1.87%, higher than the average value. The equivalent mortality rates with and without SSI for each type of surgery included in the model are presented in Table HE08.

Table HE08: Perioperative mortality rates by SSI status

Surgery type	Overall mortality rate (PHE, 2017)	Mortality with SSI	Mortality without SSI
Abdominal hysterectomy	0%	0%	0%
Bile duct, liver or pancreas	1.63%	2.25%	1.56%
Breast	0.10%	0.14%	0.10%
Cholecystectomy	0%	0%	0%
CABG	1.83%	2.55%	1.77%
Cardiac (non-CABG)	2.35%	3.28%	2.29%
Cranial	2.88%	3.98%	2.78%
Gastric	1.11%	1.57%	1.09%
Hip prosthesis	0.20%	0.29%	0.20%
Knee prosthesis	0.10%	0.14%	0.10%
Large bowel	2.67%	2.50%	3.59%
Limb amputation	2.67%	2.57%	3.68%
Reduction of long bone fracture	2.25%	2.19%	3.15%
Repair of neck of femur	6.61%	8.71%	6.17%
Small bowel	3.63%	3.40%	4.86%
Spinal	0.20%	0.29%	0.20%
Vascular	3.63%	4.94%	3.46%
All surgery	1.31%	1.87%	1.30%

HE.1.2.4.2 Life expectancy

The base-case model assumes that patients who survive the perioperative phase of their surgery experience general age-related survival thereafter. National life tables for England (2014–16) were used to estimate the average life expectancy of a person at the mean age of the surgical cohort. General population EQ-5D utility values are applied to this survival expectancy (see Section HE.1.2.6.2) to estimate an expected QALY pay-off for surviving patients, which is subject to discounting by 3.5% per year.

In practice, people who undergo a surgical procedure may have risk factors that mean they are at a higher risk of mortality than the general population after surgery. To explore this, we conduct a scenario analysis in which surgery survivors face a 10% higher mortality hazard than the age-matched general population. In this scenario patients also experience a 10% reduction in utility values, to reflect their potential for higher morbidity, and therefore lower quality of life, than the general population (see Section HE.1.2.6.2).

HE.1.2.5 Screening accuracy

For the screening strategy, in which only patients who have a positive screening test for *S. aureus* will receive mupirocin, it is appropriate to model the diagnostic accuracy of screening. This is because screening tests are typically imperfect; some positive results will be false positives, as the patient does not actually carry *S. aureus,* and some negative results will be false negatives, as the patient actually does carry *S. aureus.* Screening was not part of the formal clinical evidence review for this topic, and so a full, systematic review of diagnostic accuracy evidence was not performed. Instead, we used the data that were used in the economic model developed for the initial guideline. This included 2 screening modalities: a nasal swab and culture, and a polymerase chain reaction (PCR) test.

The nasal swab and culture method is the less accurate of the 2 options. Based on the data used in the previous model (NICE, 2008), it has a sensitivity value of 68.2%, indicating the

probability that it will correctly identify a *S. aureus* carrier by returning a positive result. Its specificity is 94.5%, which is the probability that it will correct identify a non-carrier by returning a negative result. This test is readily available in NHS centres and is used in our base-case analysis.

The PCR test is more accurate than the simple nasal swab and culture. It has a sensitivity of 98.0% and a specificity of 99.8%, making it much closer to a perfect test (NICE, 2008). However, it is also significantly more expensive than the nasal swab and culture (see Section HE.1.2.7.2). This screening modality is used in a sensitivity analysis.

HE.1.2.6 Quality of life

HE.1.2.6.1 SSI utility

Experiencing an SSI will incur a negative effect on a person's quality of life. Two systematic reviews of SSI-related quality of life estimates were identified (Gheorghe et al., 2015; Badia et al., 2017), identifying SSI utility decrements used or elicited that ranged from 0.04 to 0.48. Most were found to lie in the range 0.1 to 0.3. Both reviews identified 1 EQ-5D study conducted on UK participants (Pinkney et al., 2013), in which 735 of 749 laparotomy patients completed the EQ-5D at baseline and post-operatively. SSI occurred in 184 study subjects, allowing the impact of SSI on utility to be observed. Being the closest to NICE's preferred reference case, the utility values from this study were used in our base-case model. Standard errors to characterise uncertainty were obtained from an associated study by Gheorghe et al. (2015).

The study reports EQ-5D utility weights at baseline, 7 days after surgery, and 30 days after surgery, in SSI and non-SSI patients (see Table HE09). We convert the utility decrements from baseline into utility multipliers, so they can be applied proportionately to a common baseline utility value in our model. Baseline utility is obtained from age- and sex-related UK EQ-5D mean values (Kind et al., 1999); for example, for the base-case 'all surgery' cohort (aged 70, 42% male), the baseline utility weight is 0.780. Applying the SSI and no SSI utility multipliers at 7 days and 30 days produces the model utility weights shown in the rightmost columns of Table HE09.

Table HE09: Model inputs for SSI-related utility

Time point	EQ-5D (Pinkney et al., 2013)		Utility multiplier		Base-case cohort	
	No SSI	SSI	No SSI	SSI	No SSI	SSI
Baseline	0.762	0.718	-	-	0.780	0.780
7 days	0.514	0.464	67%	65%	0.526	0.504
30 days	0.714	0.594	94%	83%	0.731	0.645

We assume that quality of life begins to recover back to its baseline level after 7 days. As we only have 2 postoperative data points (7 days and 30 days), we assume that utility recovers in a linear fashion between these time points. However, based on the Pinkney et al. (2013) study, patients take longer than 30 days to recover their quality of life in full; therefore, we would be underestimating QALY losses associated with SSI if we ceased the utility decrements at day 30. At this point, the utility of patients who did not experience an SSI is 94% of its baseline level, whereas patients who had an SSI appear to take longer to recover, with utility at only 83% of its baseline level. By extending our linear interpolation, we can estimate that it would take a person who did not experience SSI an additional 5.5 days to recover to their baseline quality of life (Figure HE02). Patients who had an SSI will take longer to recover; their line requires 21.9 additional days before utility reaches 100% of its baseline level. By this linear extrapolation, we calculate overall one-off QALY losses associated with surgery without SSI, and surgery with SSI, compared with a person who did

not undergo surgery and remained at the baseline utility value for this period. In our base-case 'all surgery' cohort, these QALY losses are 0.015 (no SSI) and 0.022 (SSI).

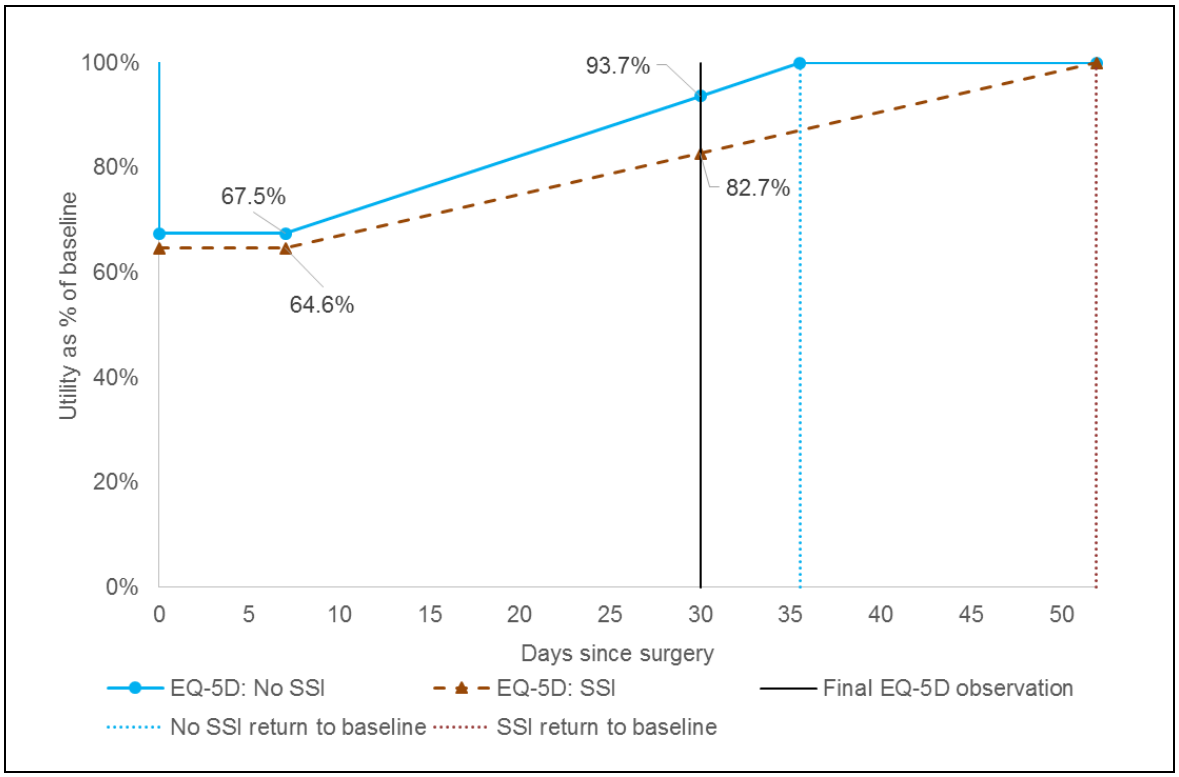


Figure HE02: Short-term quality of life recovery with and without SSI

HE.1.2.6.2 Quality-adjusted life expectancy

The base-case model assumes that baseline patient utility is equal to age- and sex-related UK EQ-5D mean values (Kind et al., 1999), and that the quality of life of a person who survives the perioperative phase returns to these general population levels after the surgery recovery period described in Section HE.1.2.6.1. The general population utility weights are presented in Table HE10. Alongside general population survival data, we estimate a QALY pay-off for surviving patients, which is subject to discounting by 3.5% per year. In the base-case analysis, for an 'all surgery' cohort aged 70 (42% male), the discounted quality-adjusted life-expectancy (QALE) for is 9.056. The total discounted QALE pay-off for a person who survives surgery is therefore 9.056 minus the surgery-related QALY loss. For a person who experiences an SSI, this value is 9.056 minus 0.022 = 8.865. For a person who does not experience an SSI, it is 9.056 minus 0.015 = 8.924.

People who die in the perioperative period are assumed to get zero QALYs. This simplification will slightly favour more effective *S. aureus* nasal decolonisation strategies, as in reality, perioperative deaths – which are more likely if there is an SSI – will not all occur immediately. Some will occur at any number of days up to 30 days after surgery.

Table HE10: UK population EQ-5D norms (Kind et al., 1999)

Age range	Men	Women
Age < 25 years	0.94	0.94
25 ≤ age < 35	0.93	0.93
35 ≤ age < 45	0.91	0.91
45 ≤ age < 55	0.84	0.85
55 ≤ age < 65	0.78	0.81
65 ≤ age < 74	0.78	0.78
75 ≤ age	0.75	0.71

In practice, people who undergo a surgical procedure may have risk factors that mean they are at a higher risk of mortality than the general population. To explore this, we conduct a scenario analysis in which surgery survivors experience a 10% reduction in their baseline utility, to reflect their potential for higher morbidity, and therefore lower quality of life, than the general population. In this scenario, their quality of life recovers in the same profile shown in Figure HE02, but returns to a lower baseline value. This reduces the QALY loss associated with SSI in absolute terms. In this scenario, we also apply a 10% higher mortality hazard than the age-matched general population, as people who undergo a surgical procedure may have risk factors that mean they are at a higher risk of mortality than the general population after surgery.

HE.1.2.7 Costs

HE.1.2.7.1 Nasal decolonisation treatment

The cost of mupirocin nasal ointment was informed by the NHS drug tariff (part VIIIA, May 2018). The committee advised that one 3 gram tube would be sufficient for a regular preoperative course of mupirocin, costing £4.24 per unit. The cost of chlorhexidine body wash was informed by the BNF (2018), as no drug tariff cost is available. The committee advised that a 125 ml bottle will usually be sufficient, costing £1.50.

The guideline development committee advised that nasal decolonisation treatment, such as mupirocin, is self-administered by a patient. Similarly, for chlorhexidine body wash, the product is provided to patients who then use it independently in the days leading up to surgery. We therefore assume there is no cost associated with treatment administration.

In a scenario analysis, 4 minutes of nurse administration time per day is assumed to be required (30 seconds to apply per nostril plus 1 minute of squeezing the nose, twice per day), for 5 days. An hourly nurse cost of £37 (PSSRU, 2017) means this equates to a nurse administration cost of £2.47 per day, which is £12.33 per course of mupirocin.

HE.1.2.7.2 Screening for *S. aureus*

For the screening strategy, in which only patients who have a positive screening test for *S. aureus* will receive mupirocin, it is appropriate to apply a cost associated with screening. For the base-case, nasal swab and culture method, this cost was obtained from the present guideline committee; a mean average of £6.66 (standard deviation: 1.97). To apply a cost associated with a nurse preparing, administering and sending off the swab, the cost from the initial model of £2.55 (NICE, 2018) was inflated to current prices (£3.32) using hospital and community health services (HCHS) inflation indices between 2004-5 and 2016-17 (PSSRU, 2017). The total cost is therefore £9.98 per screening test.

The PCR test is more accurate than the simple nasal swab and culture (see Section HE.1.2.5); however, it is also significantly more expensive. A unit cost for PCR was not obtained from the present guideline committee. Instead, the cost used in the initial model

(£19.40; NICE, 2018) was inflated to current prices (£25.25) using HCHS inflation indices between 2004-5 and 2016-17 (PSSRU, 2017). With the addition of £3.32 for nurse administration and associated tasks, the total cost is £28.56 per PCR test. This screening modality is used in a sensitivity analysis.

HE.1.2.7.3 SSI

The study from an English hospital (Jenks et al., 2014) collected resource use data in patients who did and did not experience an SSI, to identify the additional resources attributable to an SSI across different types of surgery. This was reported as the median number of additional hospital bed days required, with a 95% confidence interval. We used these data to approximate the mean excess bed days due to SSI for each type of surgery (using formula 11 [page 9] in Luo et al. (2015); see Table HE11). We then estimated the average cost per bed day due to infection using NHS reference costs 2016-17 (£312.23; see Table HE12). By multiplying the estimated mean number of excess bed days due to SSI with the cost per excess bed day, we obtained our base-case costs per SSI for each type of surgery (Table HE11). By this approach, SSIs are the most costly in gastric surgery (29.0 additional bed days, costing £9,056) and the least costly in breast surgery (2.6 additional bed days, costing £823).

Jenks et al. (2014) also undertook their own cost analysis to quantify the additional resources required to manage an SSI, reporting median costs and 95% confidence intervals. As this is a single centre, we have taken the above approach of using national level unit costs in the base-case model. However, in a scenario analysis we use the Jenks et al. costs directly, estimating their mean values and inflating them to reflect current prices using the HCHS inflation indices for 2011-12 and 2016-17 (PSSRU, 2017). These costs are higher than our base-case values, which will favour the cost-effectiveness of nasal decolonisation. Our base-case values are therefore conservative for the cost effectiveness of nasal decolonisation; if treatment is cost effective at these SSI cost values, it will certainly be cost effective if the higher values are used.

Table HE11: Excess resource use and cost associated with SSI

Surgery type	Base-case analysis			Scenario analysis		
	SSI bed days		Total cost	SSI cost		Total cost
	Median, (95% CI)[1]	Estimated mean[2]	Mean * cost day	Median, (95% CI)[1]	Estimated mean	Inflated to 2016-17[3]
Abdominal hysterectomy	14 (NR)	14.0	£4372	£5983 (NR)	£5983	£5983
Bile duct, liver or pancreas	12 (4, 24)	13.5	£4210	£2838 (-141, 14218)	£2838	£5946
Breast	3 (1, 4)	2.6	£823	£1469 (1123, 4058)	£1469	£2286
Cholecystectomy	8 (NR)	8.0	£2498	£6236 (NR)	£6236	£6236
CABG [4]	23 (19, 30)	24.1	£7515	£11003 (8517, 15395)	£11003	£11679
Cardiac (non-CABG) [4]	23 (19, 30)	24.1	£7515	£11003 (8517, 15395)	£11003	£11679
Cranial	1 (-3, 17)	5.5	£1707	£2662 (5, 20297)	£2662	£8237
Gastric	29 (NR)	29.0	£9056	£21493 (NR)	£21493	£21493
Hip prosthesis	17 (1, 57)	25.8	£8068	£3214 (657, 17040)	£3214	£7363
Knee prosthesis	7 (NR)	7.0	£2186	£2356 (NR)	£2356	£2356
Large bowel	11 (5, 13)	9.6	£2993	£4928 (4020, 7503)	£4928	£5518
Limb amputation	10 (NR)	10.0	£3123	£6799 (NR)	£6799	£6799
Reduction long bone fracture	5 (0, 32)	12.9	£4038	£4982 (284, 11873)	£4982	£5773
Repair of neck of femur	19 (NR)	19.0	£5933	£12104 (NR)	£12104	£12104
Small bowel	12 (6, 26)	14.9	£4653	£6198 (-424, 9254)	£6198	£4905
Spinal	13 (6, 27)	15.6	£4865	£7076 (3391, 17945)	£7076	£9721
Vascular	10 (5, 22)	12.6	£3824	£2480 (-757, 9209)	£2480	£3760
All surgery	10 (7, 13)	10.0	£3123	£5239 (4622, 6719)	£5239	£5542

Notes:

(1) From single English hospital study: Jenks et al. (2014).

(2) Means approximated using Luo et al. (2015) [formula 11, page 9]. Where no confidence interval was reported by the study, the median value is used.

(3) HCHS inflation indices 2011-12 (282.5) and 2016-17 (302.3) from PSSRU (2017). We have assumed 2011-12 base year based on the publication acceptance date.

(4) The single hospital study (Jenks et al., 2014) reported cardiac and CABG surgeries together, therefore the same data are used for both types of surgery.

Key: CABG, coronary artery bypass graft; CI, confidence interval; NR, not reported.

Table HE12: NHS reference costs (2016-17) for infection-related excess bed days

Reference cost code	Elective procedure		Emergency procedure	
Infections or other complications of procedures	**Mean cost**	**Activity**	**Mean cost**	**Activity**
WH07A: Multiple interventions, CC Score 2+	£311	178	£303	1842
WH07B: Multiple interventions, CC Score 0-1	£333	683	£338	2610
WH07C: Single intervention, CC Score 2+	£361	167	£285	1275
WH07D: Single intervention, CC Score 0-1	£344	567	£287	3014
WH07E: Without interventions, CC Score 4+	£322	132	£312	554
WH07F: Without interventions, CC Score 2-3	£268	532	£295	3963
WH07G: Without Interventions, CC Score 0-1	£379	1787	£312	15300
Activity-weighted average	**£312**			

Key: CC, complication and comorbidity.

HE.1.3 Results

HE.1.3.1 Deterministic base case

The base-case, deterministic analysis found that providing nasal decolonisation to patients with mupirocin dominates both the 'screen and treat if positive' and standard care (chlorhexidine wash only) strategies. This means the total cost per patient associated with universal mupirocin is lower than the alternative strategies, and it is expected to generate more QALYs per patient (Table HE13). The small QALY gain is attributable to fewer SSIs on the universal mupirocin arm, meaning quality of life after surgery recovers quicker for those patients on average, and there is less SSI-related mortality.

The 'screen and treat if positive' strategy generates fewer QALYs because a small number of patients who carry *S. aureus* are missed by imperfect screening, and therefore do not receive nasal decolonisation and remain subject to a higher, carrier risk of *S. aureus* SSI. However, the additional cost of screening all patients exceeds the cost saving by avoiding the unnecessary treatment of non-carriers, leading to higher costs overall. The standard care strategy produces the lowest total QALYs, because there is no reduction in the risk of SSI, and incurs the highest cost – despite having no nasal decolonisation or screening – due to the high cost of managing SSIs.

Table HE13: Base case cost–utility model results – all surgery cohort

	Total (discounted)		*Incremental*		*ICER*
Strategy	**Costs**	**QALYs**	**Costs**	**QALYs**	***(£/QALY)***
Universal mupirocin	£43	8.5745			
Screen & mupirocin if positive	£55	8.5744	£12	−0.00010	dominated
Standard care	£56	8.5741	£13	−0.00031	dominated

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

HE.1.3.2 Sensitivity analysis

HE.1.3.2.1 Probabilistic analysis

Figure HE03 shows the cost-effectiveness acceptability curve (CEAC) from 5,000 probabilistic model runs in the bas-case, all surgery cohort. For every model run, each input parameter was randomly sampled from its underlying distribution (HE.3). The CEAC shows the resulting probability that each strategy was cost effective at different values of 1 QALY (£0, where only cost savings are considered important, to £50,000, where QALY gains are more valuable). In a situation where no value was placed on additional QALYs gained, universal mupirocin would be 99.8% likely to be cost-effective due to its likely cost savings. It is therefore almost certain to be cost effective in any situation where QALYs are considered to be valuable (e.g. £20,000 per QALY gained). The other 2 strategies are almost certain to be cost ineffective.

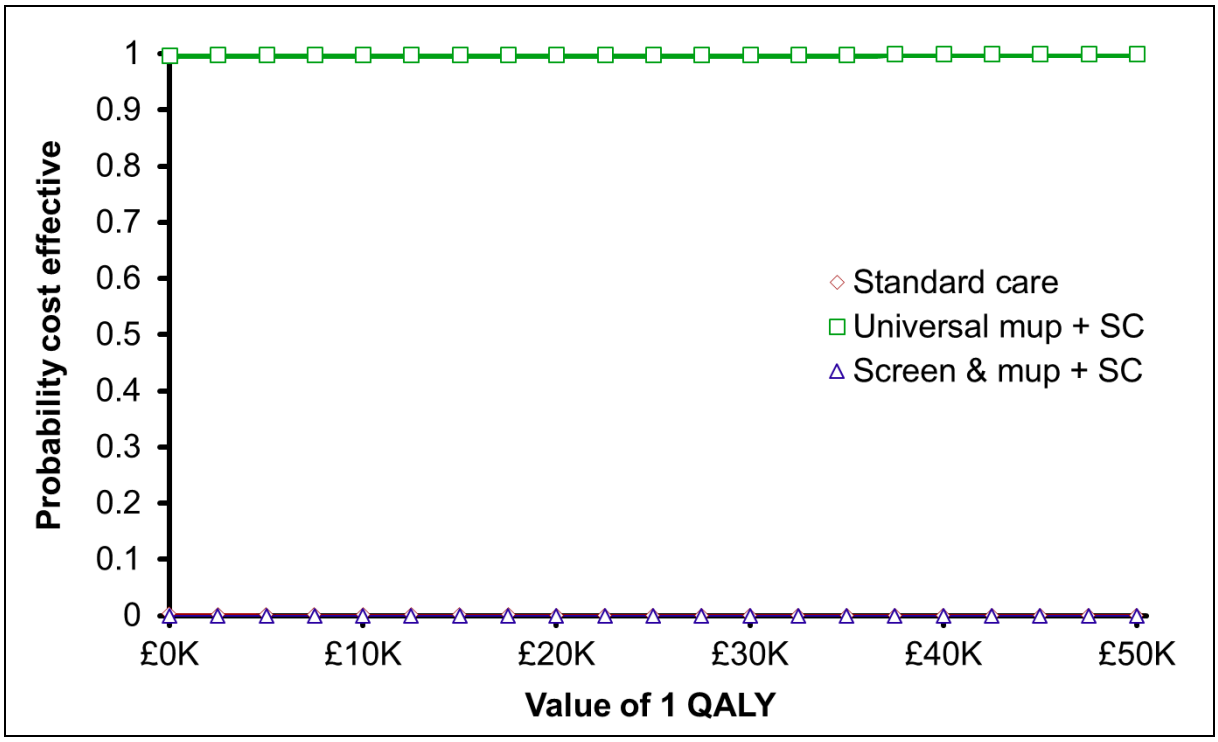


Figure HE03: CEAC from 5,000 probabilistic model runs (all surgery cohort)

HE.1.3.2.2 One-way sensitivity analysis

Figure HE04 presents the results of one-way sensitivity analysis in the form of a tornado diagram. In this analysis, each model parameter was individually varied to plausible upper and lower values determined by its underlying distribution (for example 95% confidence interval bounds). In the case of model settings, this involves changing a setting from the base-case assumption to an alternative scenario – for example, assuming mupirocin and chlorhexidine body wash are administered by a nurse, rather than self-administered by the patient, or using treatment effect from a random-effects meta-analysis, rather than the fixed-effect values. This allows us to observe the sensitivity of cost-effectiveness results to each individual parameter or setting. The tornado is centred on the base-case result, where universal mupirocin is cost effective, and shows the 15 model inputs that caused the biggest change to its incremental net monetary benefit (IMNB) compared with standard care. INMB is evaluated at a value of £20,000 per QALY, and a positive INMB value indicates that universal mupirocin would be associated with an ICER of better than £20,000 per QALY in incremental analysis.

This analysis suggests that only 1 model input has the propensity to change cost-effectiveness conclusions on its own, by making universal mupirocin cost ineffective compared with standard care. This is the source of data for baseline SSI rates; the single hospital surveillance study (Jenks et al., 2014) in our base-case analysis, and the PHE (2017) data in a scenario analysis. This is explored in greater detail in Section HE.1.3.4. No other input causes standard care to become the cost-effective strategy when varied between its plausible bounds.

No individual parameter causes universal mupirocin to become cost ineffective compared with the 'screen and treat if positive' strategy (Figure HE05). This includes the screening modality used, which is nasal swab and culture in the bas-case model, and the better but more expensive PCR test in the scenario analysis. Figure HE06 compares the 2 cost-ineffective strategies: 'screen and treat if positive' vs. standard care. In this head-to-head comparison the screening strategy is optimal, but 3 model inputs have the propensity to change that conclusion: the baseline SSI rate source; screening with PCR instead of swab and culture; and mupirocin being less effective than its base-case point estimate.

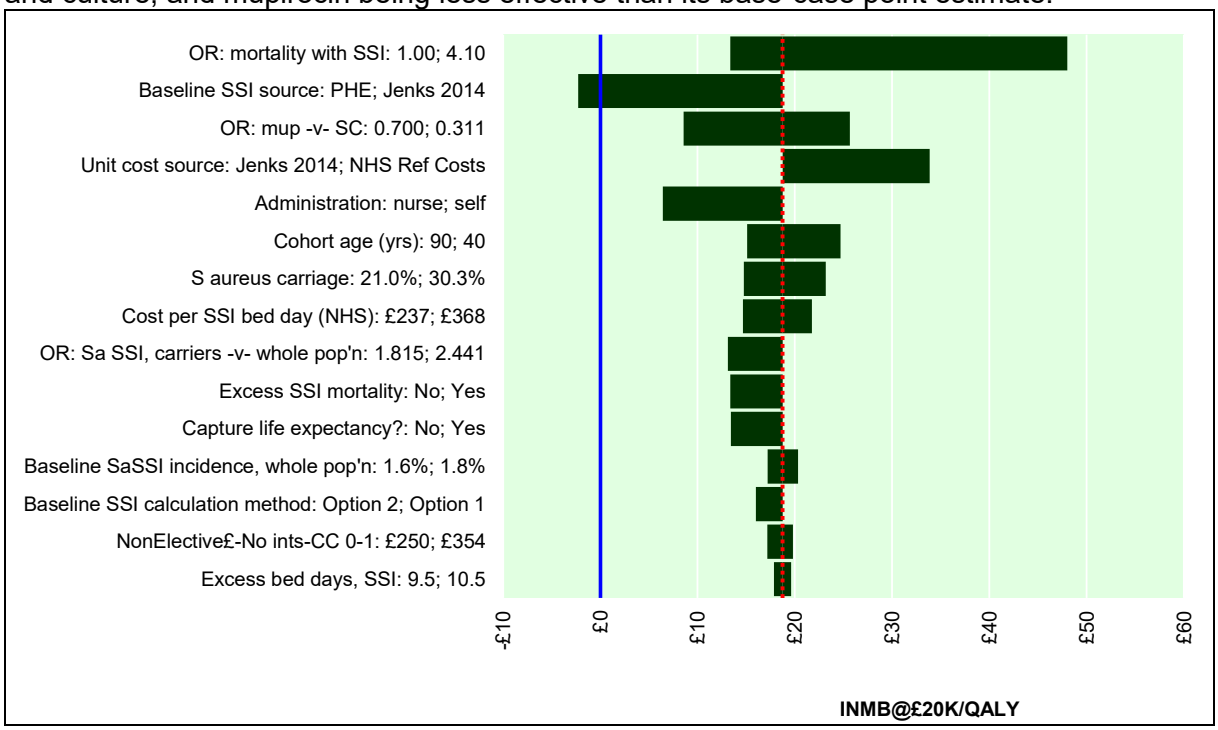


Figure HE04: One-way sensitivity analysis results (all surgery cohort) – 15 most influential parameters: universal mupirocin vs. standard care (no nasal decolonisation)

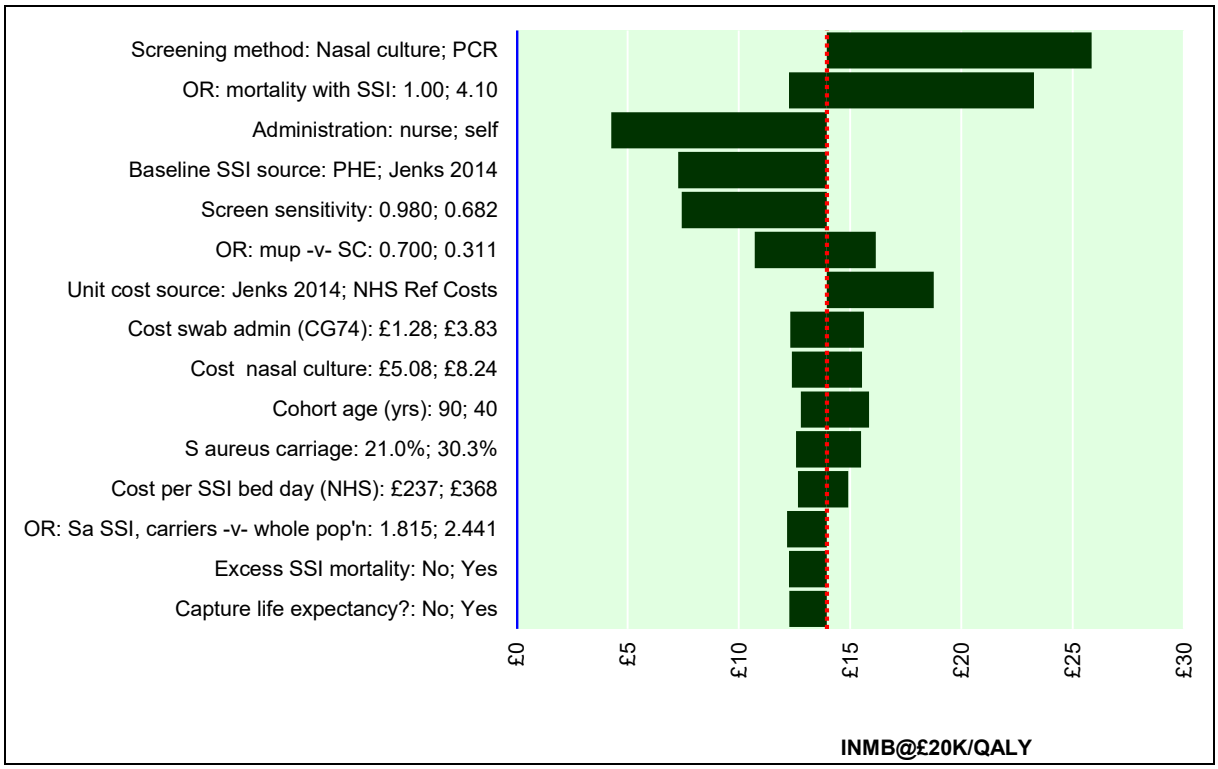


Figure HE05: One-way sensitivity analysis results (all surgery cohort) – 15 most influential parameters: universal mupirocin vs. screen & treat if positive

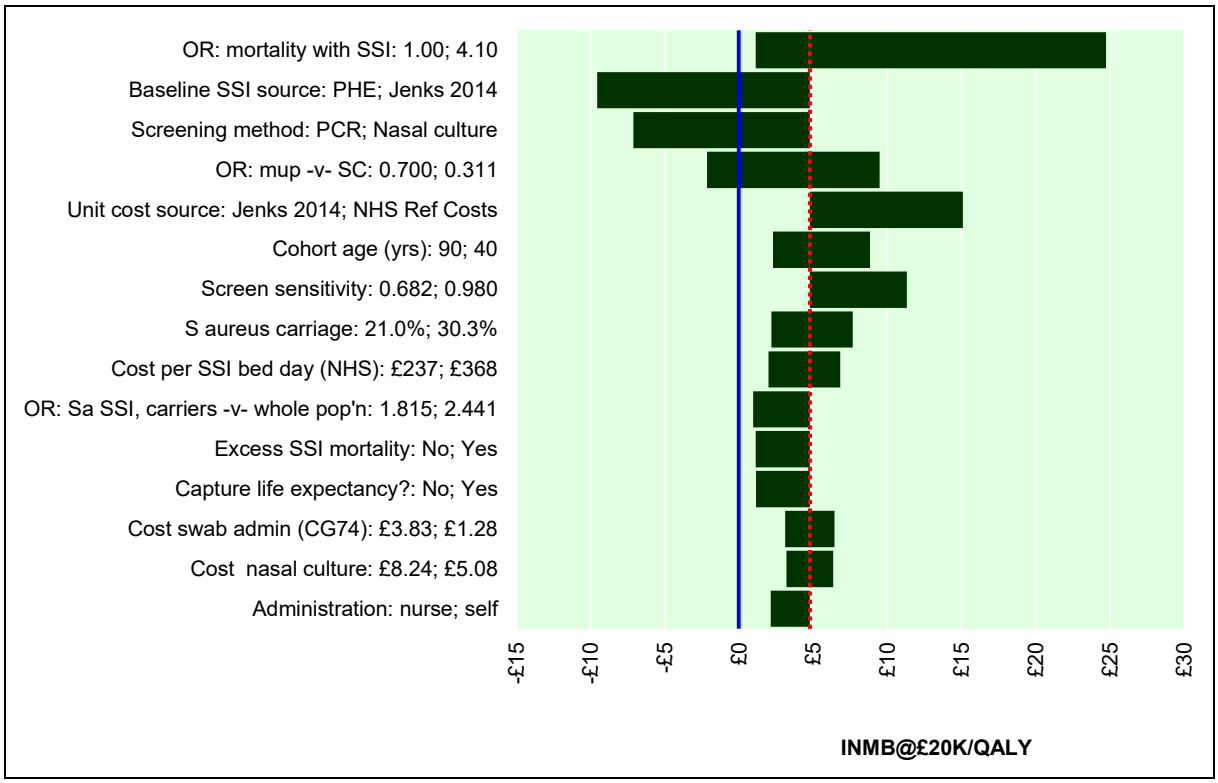


Figure HE06: One-way sensitivity analysis results (all surgery cohort) – 15 most influential parameters: screen & treat if positive vs. standard care (no nasal decolonisation)

HE.1.3.3 Subgroup analyses

Table HE14 presents deterministic cost–utility results for each type of surgery included in the model. Choosing a different surgery changes the cohort demographics (mean age and proportion male), the baseline risk of SSI, and the baseline risk of surgery mortality. The treatment effect of nasal decolonisation is assumed to remain the same, as is the proportion of infections caused by *S. aureus.* Large differences in total QALYs between surgical specialties are primarily caused by their different mean cohort ages, and therefore life expectancy; less-so by differences in risk of surgery death. Large differences in total costs between surgical specialties are caused by the different baseline risks of SSI and different additional costs attributable to SSIs in that specialty. For example, lower-risk surgeries (e.g. orthopaedic) will typically have lower overall costs, unless an SSI in that specialty is particularly costly (e.g. gastric).

These results are largely consistent with the base-case, all surgery cohort; universal mupirocin dominates the screening and standard care strategies in 15 out of 17 specialties. In the other 2 specialties, universal mupirocin has an ICER that is better than £20,000 per QALY gained, but is not dominant. In both cases, its QALY gain comes at an additional cost per patient, because the cost saved by avoiding SSIs does not fully offset the cost incurred by providing mupirocin. In the case of breast surgery, this is because it has the lowest unit cost per SSI (see Table HE11), and so giving all patients mupirocin is marginally (<£1) more expensive than not doing so. The small QALY gain associated with mupirocin leads to an ICER of £849 per QALY gained. The ICER in cranial surgery is £13,089 per QALY gained; its combination of a low baseline SSI risk and low unit cost per SSI means the benefit of nasal decolonisation is small, albeit still cost effective.

Table HE15 presents probabilistic results for each type of surgery, showing the optimal strategy when a QALY is valued at £20,000, and the probability that that strategy is optimal from 1,000 model runs. In 14 out of 17 surgical specialties the probability that universal mupirocin is cost effective is greater than 90%, and in several cases it is effectively 100%. In breast and cranial surgery this probability is 75.4% and 65.4% respectively, reflecting the less-certain deterministic results for these subgroups (Table HE14). The probabilistic results are also less certain in spinal surgery, where universal mupirocin has a 67.0% probability of being cost effective, despite its dominant deterministic result. This is because spinal surgery has a low baseline risk of SSI, making results sensitive to the additional cost of an SSI, which is highly uncertain for spinal surgery. The base-case estimate, using data from the Jenks et al. (2014) hospital surveillance study, incurs 15.6 additional hospital bed days per SSI in spinal surgery; however, mupirocin no longer dominates the other strategies if this value is only slightly lower at 12.6 days, and its ICER exceeds £20,000 versus standard care if it is 11.3 days.

Table HE14: Deterministic cost–utility model results by surgical specialty

	Total (discounted)		*Incremental*		*ICER*
Strategy	**Costs**	**QALYs**	**Costs**	**QALYs**	***(£/QALY)***
Abdominal hysterectomy					
Universal mupirocin	£41	15.5896			
Screen & mupirocin if positive	£53	15.5895	£12	-0.00001	dominated
Standard care	£53	15.5895	£12	-0.00003	dominated
Bile duct, liver, pancreas					
Universal mupirocin	£100	12.5048			
Screen & mupirocin if positive	£119	12.5045	£19	-0.00029	dominated
Standard care	£136	12.5039	£36	-0.00091	dominated
Breast					

Strategy	Total (discounted)		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Standard care	£15	13.3798			
Universal mupirocin	£15	13.3799	£0	0.00007	£849
Screen & mupirocin if positive	£23	13.3798	£8	-0.00002	dominated
Cholecystectomy					
Universal mupirocin	£83	15.0316			
Screen & mupirocin if positive	£100	15.0316	£17	-0.00003	dominated
Standard care	£110	15.0315	£28	-0.00010	dominated
CABG					
Universal mupirocin	£197	8.9786			
Screen & mupirocin if positive	£229	8.9783	£32	-0.00027	dominated
Standard care	£273	8.9777	£77	-0.00085	dominated
Cardiac, non-CABG					
Universal mupirocin	£197	10.6838			
Screen & mupirocin if positive	£229	10.6834	£32	-0.00040	dominated
Standard care	£273	10.6825	£77	-0.00126	dominated
Cranial					
Standard care	£7	12.8109			
Universal mupirocin	£10	12.8111	£2	0.00018	£13,089
Screen & mupirocin if positive	£17	12.8110	£7	-0.00006	dominated
Gastric					
Universal mupirocin	£90	12.1966			
Screen & mupirocin if positive	£108	12.1965	£19	-0.00009	dominated
Standard care	£123	12.1963	£34	-0.00028	dominated
Hip prosthesis					
Universal mupirocin	£37	8.6853			
Standard care	£47	8.6853	£10	-0.00003	dominated
Screen & mupirocin if positive	£48	8.6853	£11	-0.00001	dominated
Knee prosthesis					
Universal mupirocin	£22	8.6747			
Standard care	£25	8.6746	£3	-0.00004	dominated
Screen & mupirocin if positive	£31	8.6747	£9	-0.00001	dominated
Large bowel					
Universal mupirocin	£96	9.4273			
Screen & mupirocin if positive	£115	9.4269	£19	-0.00045	dominated
Standard care	£129	9.4259	£33	-0.00141	dominated
Limb amputation					
Universal mupirocin	£38	9.2959			
Standard care	£49	9.2954	£10	-0.00054	dominated
Screen & mupirocin if positive	£50	9.2958	£11	-0.00017	dominated

Strategy	Total (discounted)		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Reduction of long bone fracture					
Universal mupirocin	£25	11.8346			
Standard care	£30	11.8343	£5	-0.00027	dominated
Screen & mupirocin if positive	£35	11.8345	£10	-0.00009	dominated
Repair of neck femur					
Universal mupirocin	£38	3.9865			
Standard care	£49	3.9862	£11	-0.00029	dominated
Screen & mupirocin if positive	£50	3.9864	£11	-0.00009	dominated
Small bowel					
Universal mupirocin	£107	11.8653			
Screen & mupirocin if positive	£128	11.8647	£21	-0.00056	dominated
Standard care	£147	11.8636	£39	-0.00175	dominated
Spinal					
Universal mupirocin	£17	14.1742			
Standard care	£18	14.1742	£1	-0.00002	dominated
Screen & mupirocin if positive	£25	14.1742	£8	-0.00001	dominated
Vascular					
Universal mupirocin	£70	7.2068			
Screen & mupirocin if positive	£86	7.2065	£16	-0.00027	dominated
Standard care	£94	7.2059	£24	-0.00085	dominated

Note: Large differences in QALYs between different surgical specialties reflect differences in the mean cohort age, and therefore life expectancy, between surgery types.

Key: CABG, coronary artery bypass graft; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table HE15: Probabilistic cost–utility model results by surgical specialty (1,000 model runs)

Surgery type	Optimal strategy (£20k per QALY)	Probability optimal
Abdominal hysterectomy	Universal mupirocin	99.9%
Bile duct, liver, pancreas	Universal mupirocin	99.9%
Breast	Universal mupirocin	75.4%
Cholecystectomy	Universal mupirocin	99.7%
CABG	Universal mupirocin	100.0%
Cardiac, non-CABG	Universal mupirocin	99.9%
Cranial	Universal mupirocin	65.4%
Gastric	Universal mupirocin	100.0%
Hip prosthesis	Universal mupirocin	90.2%
Knee prosthesis	Universal mupirocin	95.4%
Large bowel	Universal mupirocin	100.0%
Limb amputation	Universal mupirocin	99.9%
Reduction of long bone fracture	Universal mupirocin	97.1%

Surgery type	*Optimal strategy (£20k per QALY)*	*Probability optimal*
Repair of neck femur	Universal mupirocin	99.4%
Small bowel	Universal mupirocin	100.0%
Spinal	Universal mupirocin	67.0%
Vascular	Universal mupirocin	100.0%

Key: CABG, coronary artery bypass graft; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

HE.1.3.4 Scenario analysis

A scenario analysis using the PHE data as the baseline SSI data source found that providing nasal decolonisation to patients with mupirocin had an incremental cost of £3, and an incremental QALY of 0.00003, resulting an ICER of over £100,000/QALY. The 'screen and treat if positive' strategy however, was dominated.

Table HE16: Scenario analysis when using the PHE SSI incidence data

Strategy	*Total (discounted)*		*Incremental*		*ICER (£/QALY)*
	Costs	**QALYs**	**Costs**	**QALYs**	
Standard care	£6	8.5751			
Universal mup + SC	£9	8.5751	£3	0.00003	£107,018
Screen & mup + SC	£16	8.5751	£7	-0.00001	dominated

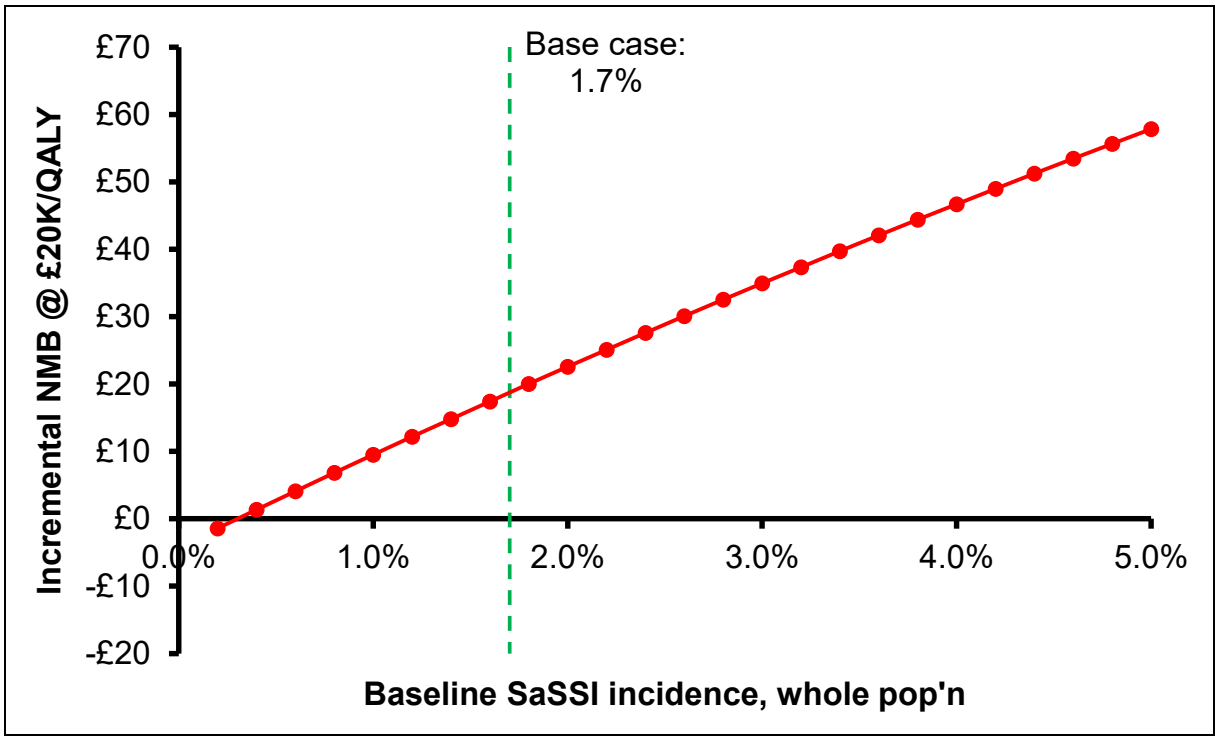


Figure HE07: Pairwise threshold analysis of the universal mupirocin vs standard care at an INMB @ £20k/QALY where the baseline SSI incidence in the whole population is varied

A pairwise threshold analysis of universal mupirocin vs standard care at an INMB @ £20,000 per QALY where the baseline SSI incidence in the whole population is varied found that the

baseline SSI incidence had to be above around 0.3% for the INMB to be positive, and for the universal mupirocin treatment to have an ICER below £20,000 per QALY.

HE.1.3.5 Threshold analysis

We undertook threshold analyses around some other important parameters, to determine how different they would need to be for our base-case cost-effectiveness conclusions to change. First, we considered the input for the underlying prevalence of *S. aureus* carriage in the population of surgical patients. In the base-case analysis this input takes a value of 25%, informed by 3,156 UK observations in a large European cross-sectional study (den Heijer et al., 2013). Universal nasal decolonisation will be less cost effective if the prevalence of *S. aureus* carriage in the surgical population is lower, because this would mean more patients receive treatment from which they receive no benefit. Figure HE08 shows the INMB of universal mupirocin compared with standard care at different values for prevalence of *S. aureus* carriage, from 5% to 95%. It indicates that universal mupirocin with chlorhexidine body wash remains cost effective unless the prevalence of *S. aureus* carriage falls below 5%, which lies outside the 95% confidence interval of our base-case estimate (20–30%).

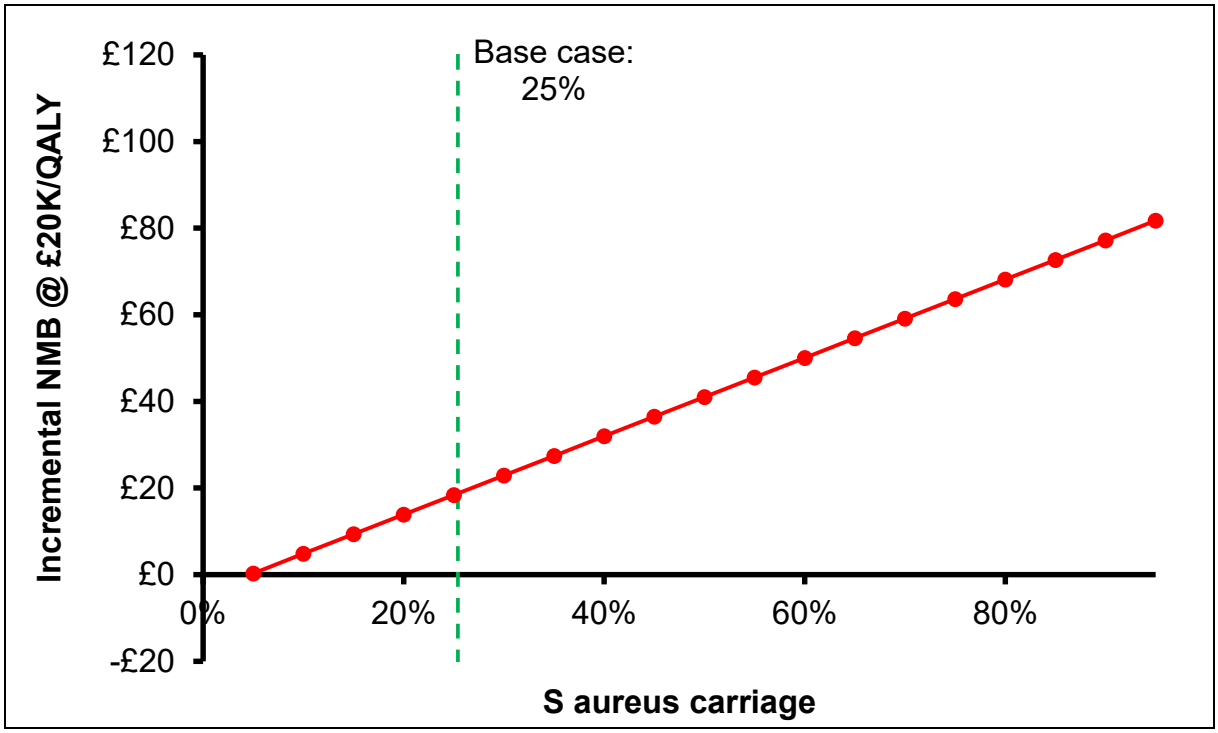


Figure HE08: *S. aureus* carriage prevalence threshold analysis (all surgery cohort) – universal mupirocin vs. standard care (no nasal decolonisation)

We also undertook a threshold analysis around the additional probability of mortality if patients contract an SSI. A pairwise threshold analysis of the universal treatment strategy vs standard care at an INMB @ £20k/QALY showed that even when the odds ratio was 1, representing no additional risk of death for patients with an SSI as compared to those without an SSI, the universal treatment strategy still maintains a positive INMB. The threshold also found a positive linear relationship for INMB as the OR of mortality with an SSI increases.

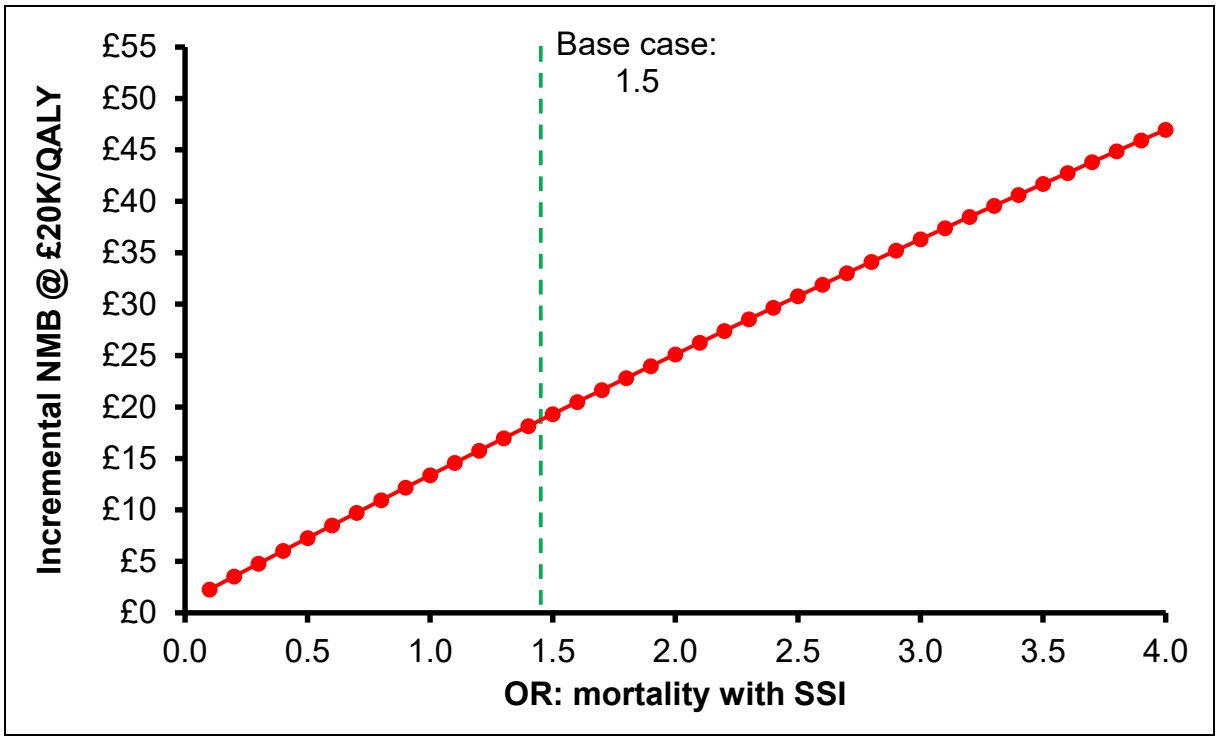


Figure HE09. Pairwise threshold analysis of the universal mupirocin vs standard care at an INMB @ £20k/QALY where the odds ratio of mortality with an SSI is varied

HE.2 RQ2

HE.2.1 Decision problem

People who contract an SSI have a higher risk of mortality, lower quality of life, and increased cost of management than those who do not contract an SSI.

New clinical trial evidence is now available looking at different preoperative skin antiseptics that was not available at the time of original guideline development. This evidence may allow for consideration of different active antiseptics and also different preparations of those antiseptics, such as provision via aqueous or alcoholic solution, and single or double application. New skin antiseptic treatment options include proprietary interventions, which may have cost implications compared with generic antiseptics. The committee advised that there is variation in current NHS practice on the use of skin antiseptics, particularly the utility of double application, which doubles treatment costs. Given the volume of surgical procedures conducted in the NHS, and with the presence of proprietary interventions, it was agreed that recommendations that seek to standardise practice could have important resource implications.

For these reasons, this research question (Table HE17) was prioritised by the guideline committee for original economic modelling.

Table HE17: Review question

Is the use of preoperative skin antiseptics clinically effective in the prevention of surgical site infection?

We developed an economic model to examine the effects of 4 types of perioperative skin antiseptics identified through a systematic literature review, on costs and outcomes for people undergoing surgical procedures.

This model was based on the economic model developed for the review question on ‘nasal decontamination in prevention of surgical site infection’ as part of this guideline update. The methods and input parameters for both models are identical, except where stated in this report.

HE.2.2 Methods

HE.2.2.1 Model structure

This model is driven by a single parameter for each of the perioperative skin antiseptics, estimating the probability of experiencing a SSI. The relationship between the number of SSIs, health-related quality of life, and cost of the management was always linear.

The analysis used a patient perspective for outcomes and an NHS+PSS perspective for costs, in line with *Developing NICE guidelines* (2014). All costs and outcomes are assumed to have occurred in the first year, therefore costs or effects beyond the first year to which discounting would apply are not considered. All calculations were undertaken in Microsoft Excel.

HE.2.2.2 Modelled population(s) and intervention(s)

The modelled populations represent a cohort of people who may undergo 17 different categories of surgery, which are associated with different SSI rates (ranging from 1.0% to 13.0%), different patient demographics (mean age ranging from 51 to 84) and different mortality risks (ranging from 0.0% to 6.2%).

The 4 modelled perioperative skin antiseptics agents are aqueous iodine, iodine + alcohol, aqueous chlorhexidine and chlorhexidine + alcohol.

Table HE18. PICO

Population	People of any age undergoing any surgery, including minimally invasive surgery (arthroscopic, thoracoscopic and laparoscopic surgery)
Intervention and comparators	• Aqueous iodine • Chlorhexidine in alcohol • Povidone Iodine in alcohol • Aqueous Chlorhexidine
Outcomes	• Surgical site infections (superficial, deep and organ/space SSI) (Including SSIs up to 30 days and 1 year).

HE.2.2.3 Baseline parameters

Relevant baseline model parameters are:

- age
- sex
- type of surgery
- baseline incidence of SSI

The model shared the same demographics as the nasal decontamination model – see HE.1.2.2.1.

The base-case data source for SSI incidence was Jenks et al. (2014), as for the nasal decontamination model (see HE.1.2.2.2), whilst a sensitivity analysis used the PHE SSI surveillance service data.

HE.2.2.4 Key assumptions

There are several assumptions for these economic analyses which need to be considered when analysing the results generated. These are summarised in Table HE19.

Table HE19. Key assumptions of original cost-utility model

- The perioperative skin antiseptics agents are only able to influence the incidence of SSI.
- The downstream consequences for health-related quality of life and cost of management of SSI's remain the same when an SSI occurs, regardless of which perioperative skin antiseptics agent was used.
- Each of the 4 modelled perioperative skin antiseptics agents has the same relative effect of reducing the incidence of SSI across all surgical settings.
- Each of the 4 modelled perioperative skin antiseptics agents has the same class effect, despite which product cost they are paired with.
- Where the perioperative skin antiseptics agent is a liquid, we assumed that 150ml (which represents a part of a bottle) was used in the base case. We are aware that many institutions require a full bottle to be used for each patient (which may result in significant wastage), so this was tested in a sensitivity analysis.

HE.2.2.5 Treatment effects

To generate the treatment effects for each of the antiseptic skin agents, the model combined a baseline effectiveness odds of getting an SSI with aqueous iodine with a model that estimates the antiseptic skin agents' relative efficacy as compared to the aqueous iodine.

For the base case, the effectiveness estimates (odds ratios for any SSI) were taken from the network meta-analysis undertaken for this review (see Evidence review B). Class-level effects were assumed for the 4 options, as there was no evidence in the review that different preparations, concentrations or approaches had significantly different results within each class. This approach enabled us to calculate the absolute probabilities of SSI for the perioperative skin antiseptics (shown in **Table HE25**) by combining odds ratios from the network meta-analysis with a 'baseline' risk of SSI derived from Jenks et al. (2014), using additional details provided by the investigators regarding how often each of the 4 types of skin antiseptics were used in a Plymouth hospital during the period covered by the paper (Table HE26).

Table HE20. Infection probability of aqueous iodine given the infection probability of the other 3 antiseptic agents, and the usage rate of all antiseptic agents

$$a = \frac{z - cd - ef - gh}{\mathrm{b}}$$

a = infection probability of aqueous iodine, b = proportion use of aqueous iodine, c = infection probability of chlorhexidine+alcohol, d = proportion use of chlorhexidine+alcohol, e = infection probability of aqueous chlorhexidine, f = proportion use of aqueous chlorhexidine, g = infection probability of iodine+alcohol, h = iodine+alcohol, z = overall infection rate

This resulted in the synthesis model, which estimated the 30-day odds of contracting an SSI with aqueous iodine at 0.0634.

An alternative approach to calculate the baseline odds ratio for effects, used in a sensitivity analysis, was to pool the arms of RCTs to generate a yearly rate for SSIs arising from the use of aqueous iodine (odds = 0.223).

Table HE21. Baseline risk of SSI

		Odds
Pooled RCT arms	Ln(annual rate)=0.223	0.108
Synthesis model	Ln(odds) = -2.8	0.0634

The base-case model combined the 2 parameters from the meta-regression NMA (the log odds ratio for alcohol versus aqueous, and chlorhexidine versus iodine) to generate the log odds ratios, and the odds ratios for chlorhexidine in alcohol, povidone iodine in alcohol and aqueous chlorhexidine compared with aqueous iodine (Table HE22). This was combined with a baseline effect rate of aqueous iodine to generate the resultant number of SSIs for each of the antiseptic skin agents. We used the 'lumped' NMA in a scenario analysis.

Table HE22. Relative effects in the model

Multivariate normal sampling	Mean	Standard Deviation	Mean	Standard Deviation
	Lumped model		Meta-regression model	
Ln(OR)				
Alcohol -v- aqueous			-0.186	0.132

Multivariate normal sampling	Mean	Standard Deviation	Mean	Standard Deviation
Chlorhexidine -v- iodine			-0.228	0.113
Ln(OR) -v- aqueous iodine				
Aqueous iodine	0	0	0	
Chlorhexidine in alcohol	-0.407	0.105	-0.415	
Povidone Iodine in alcohol	-0.166	0.155	-0.186	
Aqueous Chlorhexidine	-0.175	0.236	-0.228	
OR -v- aqueous iodine				
Aqueous iodine	1		1	
Chlorhexidine in alcohol	0.665		0.661	
Povidone Iodine in alcohol	0.847		0.830	
Aqueous Chlorhexidine	0.839		0.796	

To generate the parameters in probabilistic sensitivity analysis for the meta-regression model, we used multivariate normal sampling (assuming normality on a logit scale). The correlation matrix is shown in Table HE23.

Table HE23. Correlation matrix used to generate parameters for the probabilistic sensitivity analysis – meta-regression model.

	Ln(OR): alcohol -v- aqueous	Ln(OR): chlorhexidine -v- iodine
Ln(OR): alcohol -v- aqueous	1.000	–
Ln(OR): chlorhexidine -v- iodine	-0.663	1.000

A similar approach was taken for the 'lumped' NMA scenario analysis (Table HE24).

Table HE24. Correlation matrix used to generate parameters for the probabilistic sensitivity analysis – 'lumped' model.

	Ln(OR): chlorhexidine in alcohol -v- aqueous iodine	Ln(OR): iodine in alcohol -v- aqueous iodine	Ln(OR): aqueous chlorhexidine -v- aqueous iodine
Ln(OR): chlorhexidine in alcohol -v- aqueous iodine	1.000	–	–
Ln(OR): iodine in alcohol -v- aqueous iodine	0.584	1.000	–
Ln(OR): aqueous chlorhexidine -v- aqueous iodine	0.287	0.153	1.000

Table HE25. Infection probabilities

Antiseptic type	Ln (odds) Mean	Probability
Ln(odds)		
Aqueous iodine	-2.7590	0.0596
Chlorhexidine in alcohol	-3.1737	0.0402

Antiseptic type	Ln (odds) Mean	Probability
Povidone Iodine in alcohol	-2.9453	0.0500
Aqueous Chlorhexidine	-2.9873	0.0480

Table HE26. Surgeons' use of preoperative skin antiseptics in a Plymouth hospital over the study period covered by Jenks et al. (2014) (audit data)

Antiseptic class	Surgeons use of class of product (instances)	Percentage of total uses of antiseptics
Chlorhexidine + Alcohol	31	33.0%
Aqueous Chlorhexidine	11	11.7%
Chlorhexidine + Iodine	7	7.4%
Aqueous Iodine	45	47.9%

HE.2.2.6 Mortality

SSI mortality and life expectancy calculations in this model were the same as those used in the nasal decontamination model – see HE.1.2.4.

HE.2.2.7 Quality of life

Methods to calculate quality of life in this model were the same as those used in the nasal decontamination model – see HE.1.2.6.

HE.2.2.8 Costs and resource use

The guideline committee agreed that the results of the model should be presented at a class level for each of the 4 options, using the costs of a single product that is considered representative of that class in an English NHS setting.

Costs for the antiseptics (Table **HE**27) were sourced from the NHS Supply Chain catalogue (accessed August 2018).

Table HE27. Treatments and their costs in the model

Treatment Class	Active ingredient	Brand Name	Volume	Price	Price for 150mls
Chlorhexidine (aqueous)	Chlorhexidine 4%	HiBiScrub	500 ml	£3.80	£1.14
Chlorhexidine (alcohol)	Chlorhexidine gluconate 2% + isopropyl alcohol 70%	ChloraPrep	Box of 25 applicators	£211.69	£8.46 per 26 ml applicator
	Chlorhexidine gluconate 2% + isopropyl alcohol 70%	ChloraPrep Tint	Box of 25 applicators	£222.36	£8.89 per 26 ml applicator
	0.5% Chlorhexidine denatured ethanol 70% solution pink	Hydrex	600 ml	£2.95	£0.74
	Chlorhexidine 2% in 70% IPA Bottle	Ecolab	500 ml	£5.76	£1.73
Iodine (aqueous)	7.5% Povidone iodine surgical scrub solution	Videne	500 ml	£5.49	£1.65

Treatment Class	Active ingredient	Brand Name	Volume	Price	Price for 150mls
Iodine (alcohol)	10% Povidone Iodine antiseptic solution	Videne Antiseptic	500 ml	£5.49	£1.65

We found only a single cost for the aqueous iodine, iodine + alcohol and aqueous chlorhexidine class of products. However, there were 4 relevant costs for the chlorhexidine + alcohol class of product. As the model assumes a class-level effect for all of these products, it would not be sensible to assess them in a single, incremental analysis, as the cheapest would always be dominant. However, the committee was interested in knowing whether the costs associated with each product would lead to different conclusions when chlorhexidine + alcohol is compared with other classes of antiseptic. Therefore, separate analyses were undertaken using the price of each of these products.

For the base-case analysis for all solutions, the guideline committee advised that 150 ml of solution should be assumed. In sensitivity analyses, we examined the effects of using 50 ml (lower value) or a full bottle (upper value: 500 ml for all solutions except 600 ml for 0.5% chlorhexidine + alcohol). The guideline committee also advised that, in all analyses involving a solution, a red-staining dye (£1.55 for 12 ml) would be added to the full bottle to help surgeons see which parts of the skin had been coated. The guideline committee also advised that, where solutions were used, 2 Rampley sponge holders would be required, each of which would need sterilisation after each patient (£1.57 per instrument).

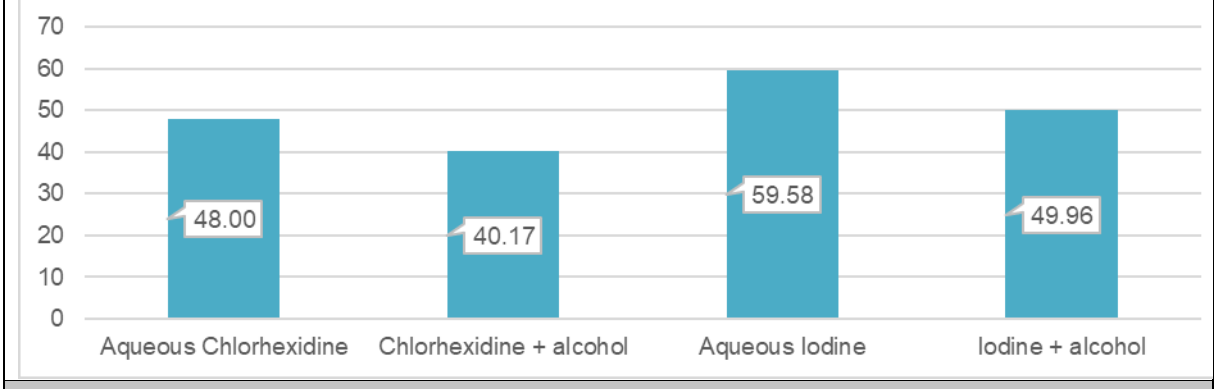
In analyses where applicators were used, the guideline committee advised that 1 applicator would be used in the base case. In sensitivity analysis, we examined the impact of number of applicators on cost–utility results. We also conducted a threshold analysis to examine the effect of a disposal costs for applicators, which are uncertain.

For parameters related to the cost of dealing with an SSI, the model used values identical to those found in the nasal decontamination model – see HE.1.2.7.3.

HE.2.3 Results

HE.2.3.1 Deterministic analyses

Chlorhexidine + alcohol is associated with the lowest number of SSIs (see Figure HE10) and, in all deterministic and probabilistic analyses (Table **HE**28, Table **HE**30), it dominates all other comparators (that is, it is associated with lower costs and greater benefits). This is true when the price of any of the 4 chlorhexidine + alcohol products is used.



Aqueous iodine is associated with the highest number of SSIs whilst chlorhexidine+alcohol is associated with the lowest number of SSIs.

Figure HE10. Number of SSIs for each class of product per 1,000 patients.

Table HE28: Original cost–utility analysis: base-case deterministic

Strategy	Absolute		Incremental			No. of SSIs per 1,000 operations
	Costs	QALYs	Costs	Costs	ICER	
Chlorhexidine + alcohol costs = 0.5% chlorhexidine in 70% alcohol (Hydrex)						
Chlorhexidine (alcohol)	£130.86	8.5728				40.17
Chlorhexidine (aqueous)	£155.72	8.5724	£24.86	-0.00045	dominated	48.00
Iodine (alcohol)	£162.34	8.5723	£31.48	-0.00056	dominated	49.96
Iodine (aqueous)	£192.39	8.5717	£61.53	-0.00111	dominated	59.58
Chlorhexidine + alcohol costs = 2% chlorhexidine in 70% alcohol (Ecolab)						
Chlorhexidine (alcohol)	£131.85	8.5728				40.17
Chlorhexidine (aqueous)	£155.72	8.5724	£23.87	-0.00045	dominated	48.00
Iodine (alcohol)	£162.34	8.5723	£30.49	-0.00056	dominated	49.96
Iodine (aqueous)	£192.39	8.5717	£60.54	-0.00111	dominated	59.58
Chlorhexidine + alcohol costs = 2% chlorhexidine in 70% alcohol 26 ml applicator (ChloraPrep)						
Chlorhexidine (alcohol)	£133.91	8.5728				40.17
Chlorhexidine (aqueous)	£155.72	8.5724	£21.81	-0.00045	dominated	48.00
Iodine (alcohol)	£162.34	8.5723	£28.43	-0.00056	dominated	49.96
Iodine (aqueous)	£192.39	8.5717	£58.48	-0.00111	dominated	59.58
Chlorhexidine + alcohol costs = 2% chlorhexidine in 70% alcohol 26 ml applicator with dye (ChloraPrep+Tint)						
Chlorhexidine (alcohol)	£134.34	8.5728				40.17
Chlorhexidine (aqueous)	£155.72	8.5724	£21.38	-0.00045	dominated	48.00
Iodine (alcohol)	£162.34	8.5723	£28.00	-0.00056	dominated	49.96
Iodine (aqueous)	£192.39	8.5717	£58.05	-0.00111	dominated	59.58

We found similar results across all types of surgery. As an example, the pairwise comparison of chlorhexidine + alcohol (with Ecolab costs) vs aqueous chlorhexidine is shown in Table HE29 for each of the 17 surgery types. The additional number of SSIs prevented with Chlorhexidine + Alcohol compared to Aqueous Chlorhexidine per 1,000 operations was directly correlated with the baseline SSI incidence from the Jenks et al. study data.

Table HE29. Pairwise comparison of chlorhexidine + alcohol vs aqueous chlorhexidine by surgery type

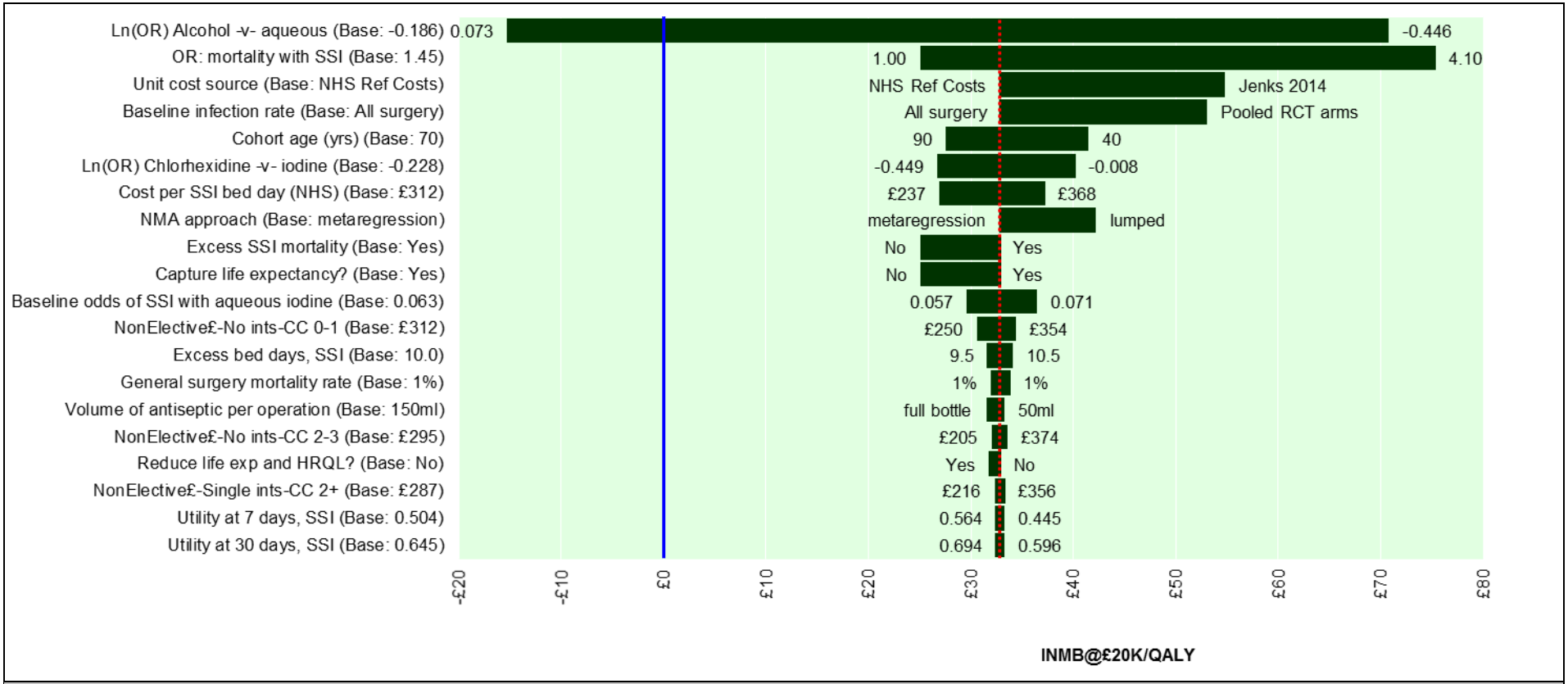
Surgery type	Incremental			Additional SSIs prevented per 1,000 operations
	Costs	QALYs	ICER	
Abdominal hysterectomy	−£23.00	0.00004	Dominant	5.39
Bile duct, liver or pancreas	−£58.30	0.00133	Dominant	13.99
Breast	−£5.50	0.00010	Dominant	7.40
Cholecystectomy	−£46.19	0.00015	Dominant	18.72
CABG	−£117.78	0.00124	Dominant	15.75
Cardiac (non-CABG)	−£117.78	0.00183	Dominant	15.75
Cranial	−£2.12	0.00026	Dominant	1.58
Gastric	−£54.59	0.00041	Dominant	6.09
Hip prosthesis	−£20.10	0.00004	Dominant	2.56
Knee prosthesis	−£10.26	0.00006	Dominant	4.96
Large bowel	−£54.44	0.00207	Dominant	18.38
Limb amputation	−£20.86	0.00078	Dominant	6.87
Reduction of long bone fracture	−£12.45	0.00040	Dominant	3.23
Repair of neck of femur	−£21.11	0.00042	Dominant	3.66
Small bowel	−£63.27	0.00256	Dominant	13.72
Spinal	−£6.97	0.00003	Dominant	1.55
Vascular	−£40.74	0.00124	Dominant	10.53

HE.2.3.2 One-way sensitivity analyses

All one-way sensitivity analyses (OSA) comparing preparations of chlorhexidine + alcohol (the agent with the lowest cost and the highest effect) with aqueous chlorhexidine (the agent with the next lowest cost and next highest effect) where a QALY is valued at £20,000, showed only one parameter, the log odds ratio of alcohol vs aqueous, when varied within its 95% credible interval, was able to reduce the INMB below £0. This reflects the fact that, at a 95% confidence level, the data are consistent with no advantage for alcoholic preparations over aqueous ones (see Evidence review B)

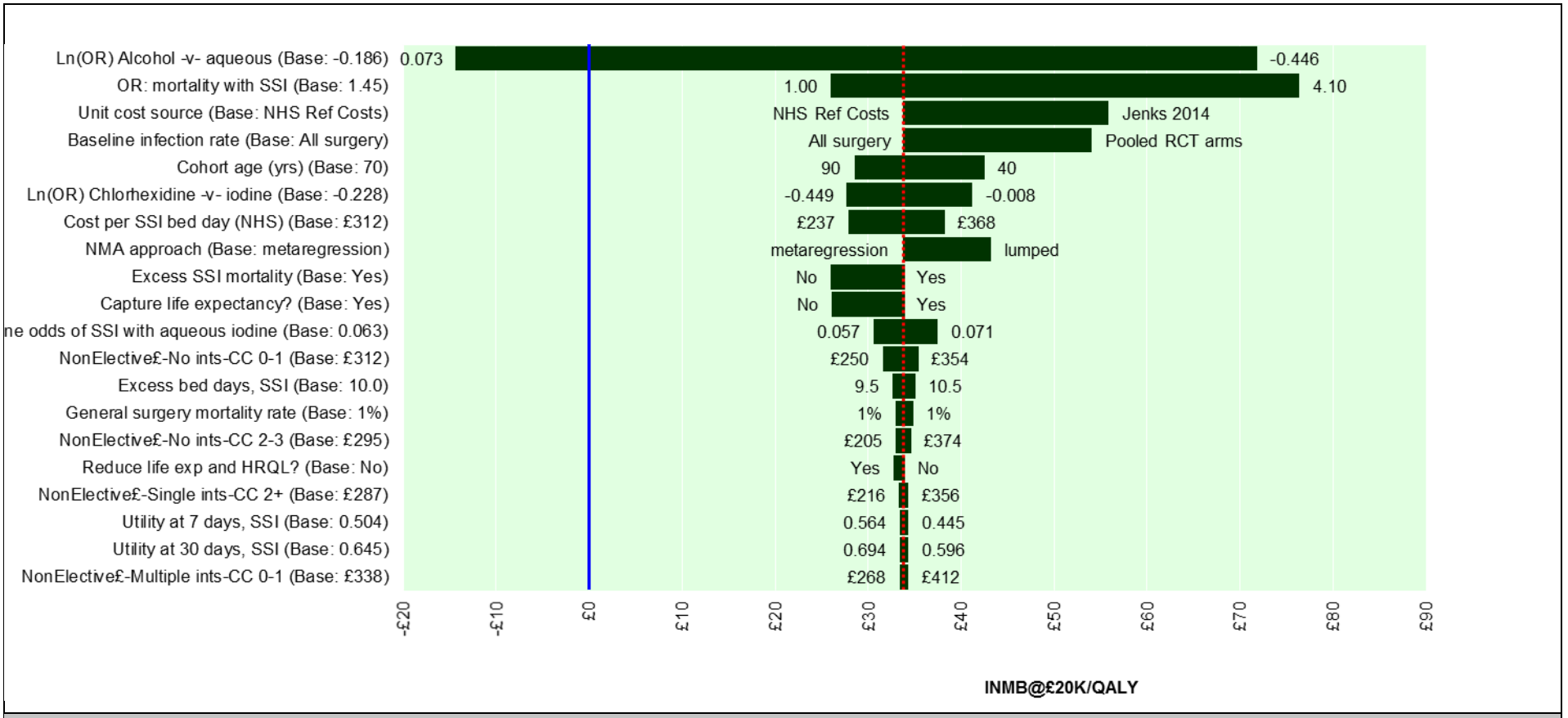
An OSA for chlorhexidine + alcohol (where the chlorhexidine + alcohol costs = 2% Ecolab) compared against iodine + alcohol where a QALY is valued at £20,000, also showed that the log odds ratio of alcohol vs aqueous, when varied to its extreme, was able to reduce the INMB below £0.

Another OSA comparing aqueous chlorhexidine vs Iodine + alcohol, where a QALY is valued at £20,000, showed that both the log odds ratio of alcohol as compared with aqueous solution, and the log odds ratio of chlorhexidine versus iodine were able to reduce the INMB below £0. This means that both parameters that drive the class effect of each of the skin antiseptics both contain enough uncertainty to change the decision of which agent to use.



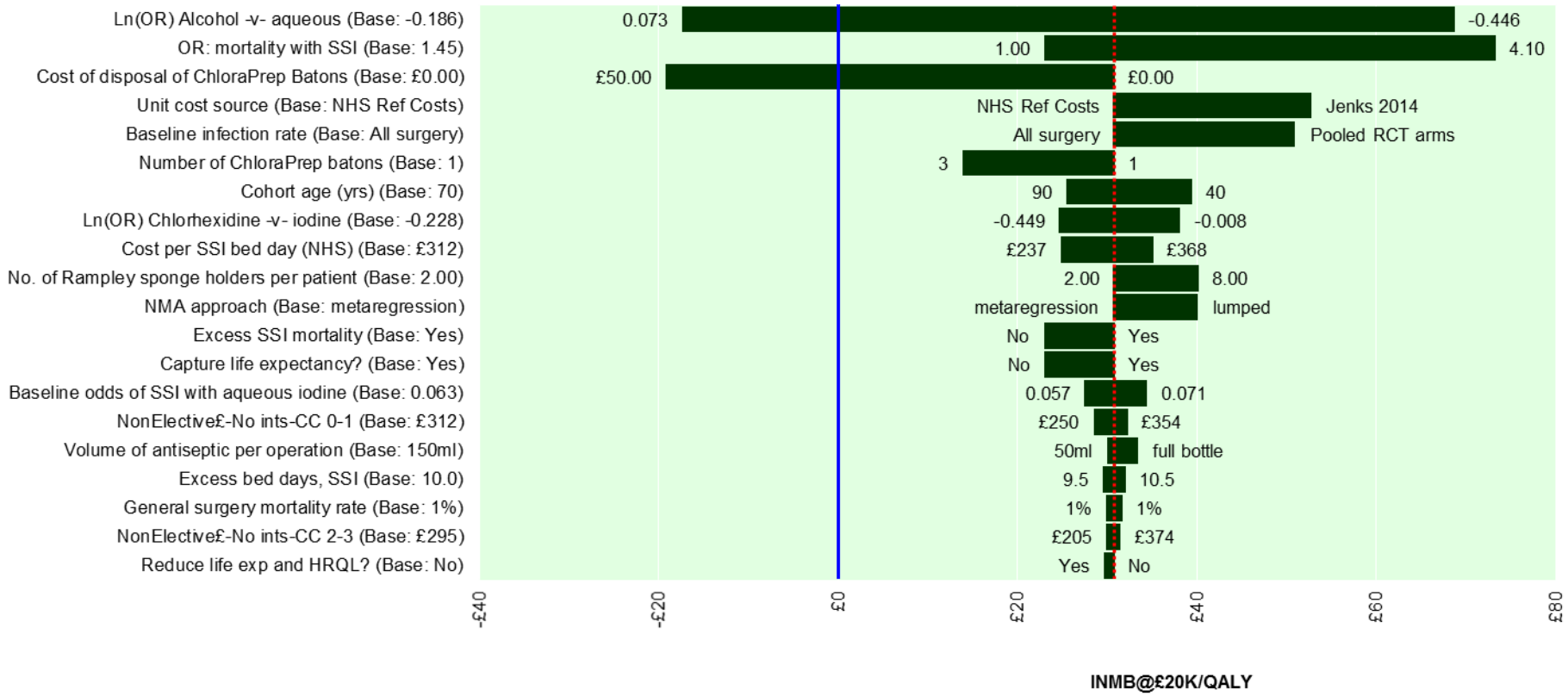
Only the parameter Ln(OR) Alcohol -v-Chlorhexidine is able to reduce the INMB to below £0.

Figure HE11. One-way sensitivity analysis for chlorhexidine + alcohol vs aqueous chlorhexidine where chlorhexidine + alcohol costs = 2% Ecolab - INBM @ £20k per QALY



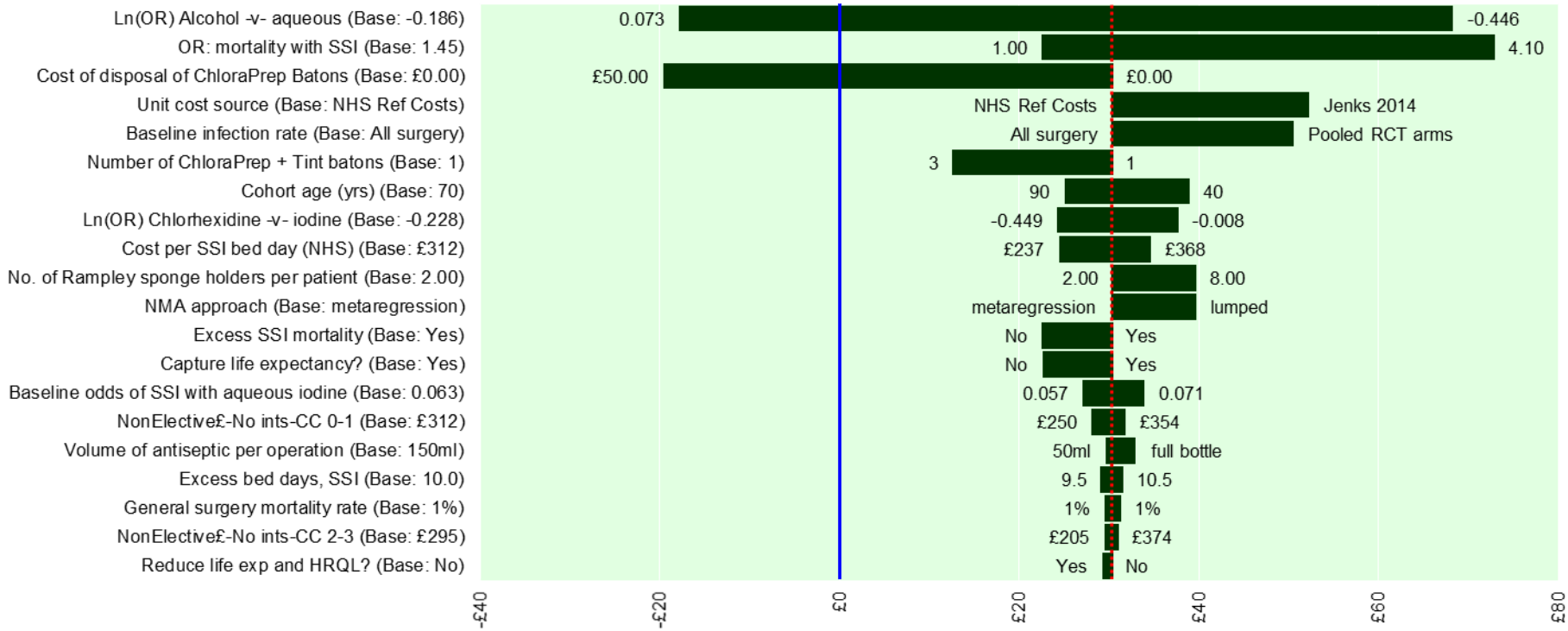
Only the parameter Ln(OR) Alcohol -v-Chlorhexidine is able to reduce the INMB to below £0.

Figure HE12. One-way sensitivity analysis for chlorhexidine + alcohol vs aqueous chlorhexidine where chlorhexidine + alcohol costs = Hydrex - INBM @ £20k per QALY



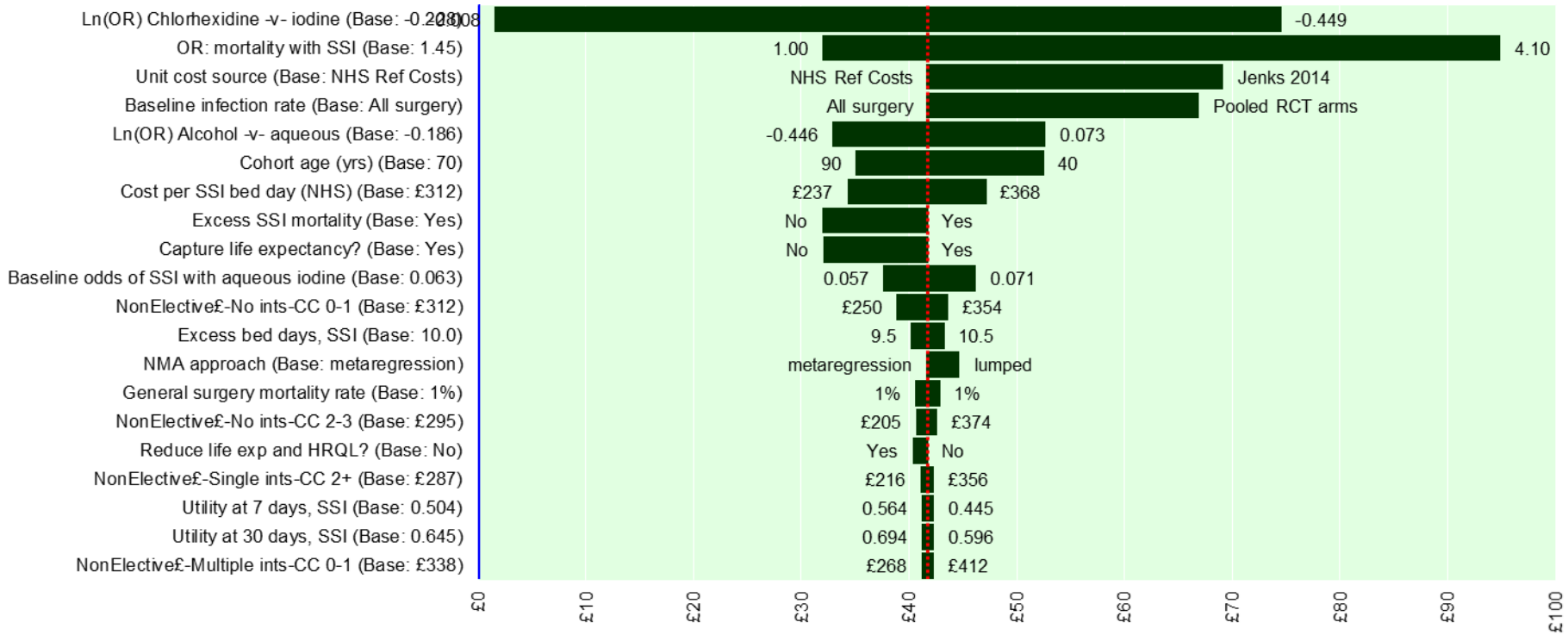
Only the parameter Ln(OR) Alcohol -v-Chlorhexidine is able to reduce the INMB to below £0.

Figure HE13. One-way sensitivity analysis for chlorhexidine + alcohol vs aqueous chlorhexidine where chlorhexidine + alcohol costs = ChloraPrep - INBM @ £20k per QALY



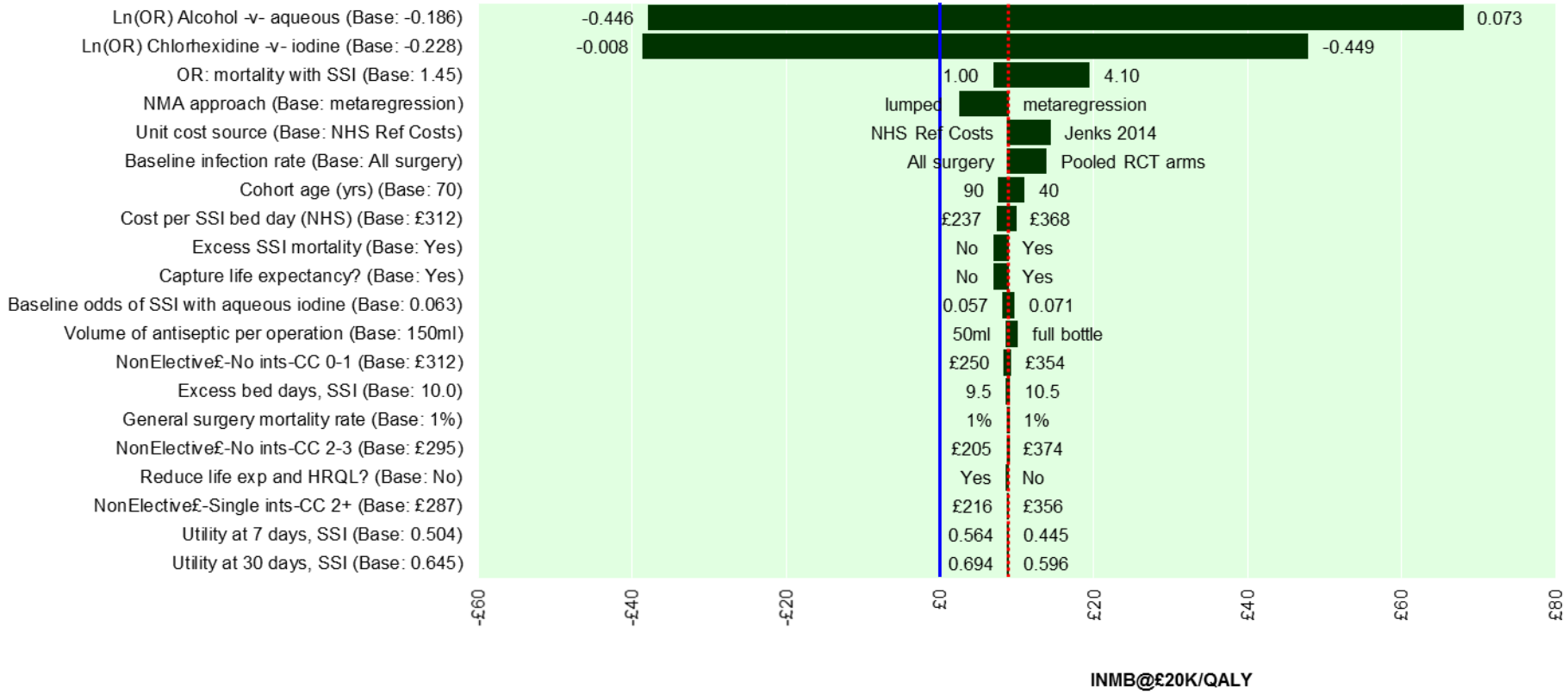
Only the parameter Ln(OR) Alcohol -v-Chlorhexidine is able to reduce the INMB to below £0.

Figure HE14. One-way sensitivity analysis for chlorhexidine + alcohol vs aqueous chlorhexidine where chlorhexidine + alcohol costs = ChloraPrep+Tint - INBM @ £20k per QALY



None of the uncertainty reflected in any of the parameters was able to reduce the INMB below £0 for Chlorhexidine + Alcohol vs Iodine + Alcohol where Chlorhexidine + Alcohol costs = 2% Ecolab at an INBM @ £20k per QALY

Figure HE15. One-way sensitivity analysis for chlorhexidine + alcohol vs iodine + alcohol where chlorhexidine + alcohol costs = 2% Ecolab - INBM @ £20k per QALY



Both the log odds ratio of alcohol versus aqueous, and log odd ratio of chlorhexidine versus iodine parameters, have sufficient uncertainty that when varied to their low extreme values, could change the treatment decision, as both easily reduce the INMB of Aqueous Chlorhexidine vs Iodine + Alcohol to below £0 (when a QALY is valued at £30k).

Figure HE16. One-way sensitivity analysis for aqueous chlorhexidine vs iodine + alcohol - INBM @ £20k per QALY

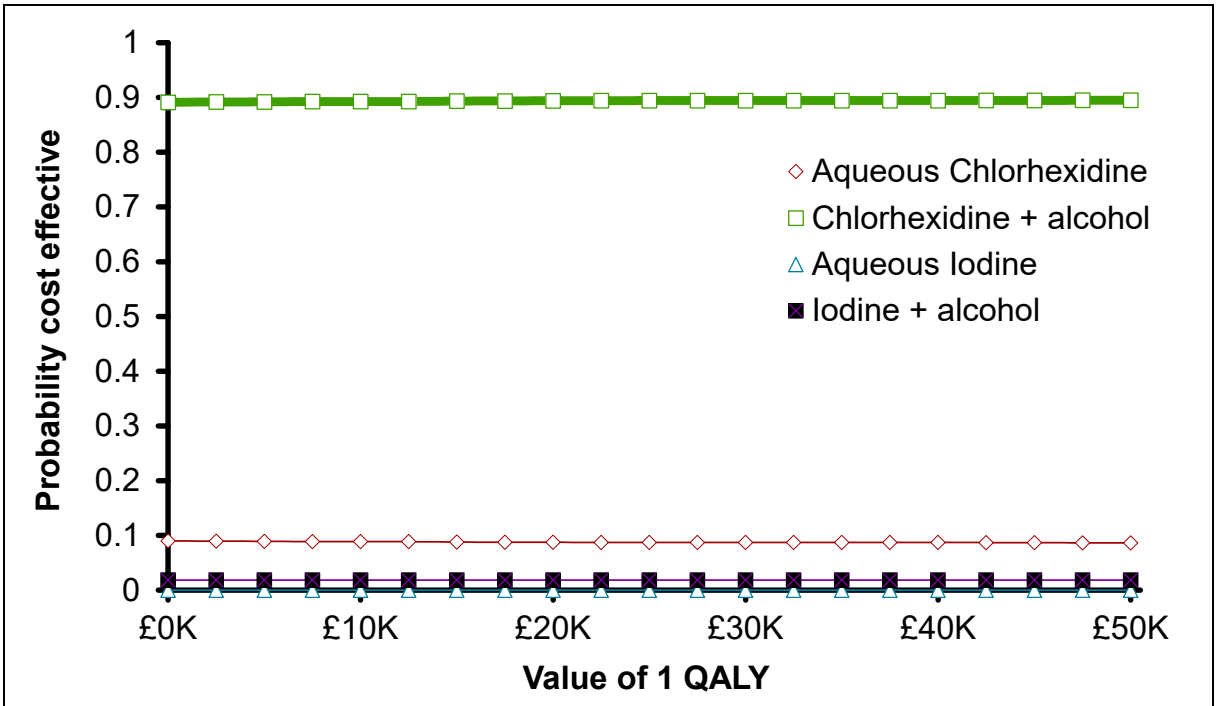
HE.2.3.3 Probabilistic analyses

Table HE30. Original cost–utility analysis: base-case probabilistic (5,000 iterations)

Strategy	Absolute		Incremental			No. of SSIs per 1,000 operations
	Costs	QALYs	Costs	Costs	ICER	
Chlorhexidine + alcohol costs = 0.5% chlorhexidine in 70% alcohol (Hydrex)						
Chlorhexidine (alcohol)	£131.78	8.56875				40.169
Chlorhexidine (aqueous)	£157.19	8.56808	£25.41	-0.00066	Dominated	48.001
Iodine (alcohol)	£163.43	8.56794	£31.65	-0.00080	Dominated	49.959
Iodine (aqueous)	£192.58	8.56717	£60.80	-0.00157	Dominated	59.580
Chlorhexidine + alcohol costs = 2% chlorhexidine in 70% alcohol (Ecolab)						
Chlorhexidine (alcohol)	£132.56	8.57335				40.45
Chlorhexidine (aqueous)	£156.44	8.57269	£23.88	-0.00066	Dominated	48.23
Iodine (alcohol)	£163.83	8.57251	£31.27	-0.00084	Dominated	50.57
Iodine (aqueous)	£192.47	8.57174	£59.91	-0.00162	Dominated	59.66
Chlorhexidine + alcohol costs = 2% chlorhexidine in 70% alcohol 26 ml applicator (ChloraPrep)						
Chlorhexidine (alcohol)	£134.77	8.56846				40.47
Chlorhexidine (aqueous)	£156.68	8.56781	£21.92	-0.00065	Dominated	48.4
Iodine (alcohol)	£163.99	8.56763	£29.22	-0.00083	Dominated	50.38
Iodine (aqueous)	£192.74	8.56687	£57.97	-0.00159	Dominated	59.65
Chlorhexidine + alcohol costs = 2% chlorhexidine in 70% alcohol 26 ml applicator with dye (ChloraPrep+Tint)						
Chlorhexidine (alcohol)	£135.15	8.57238				40.4
Chlorhexidine (aqueous)	£156.62	8.57172	£21.47	-0.00066	Dominated	48.25
Iodine (alcohol)	£163.92	8.57154	£28.76	-0.00085	Dominated	50.47
Iodine (aqueous)	£192.59	8.57077	£57.43	-0.00162	Dominated	59.69

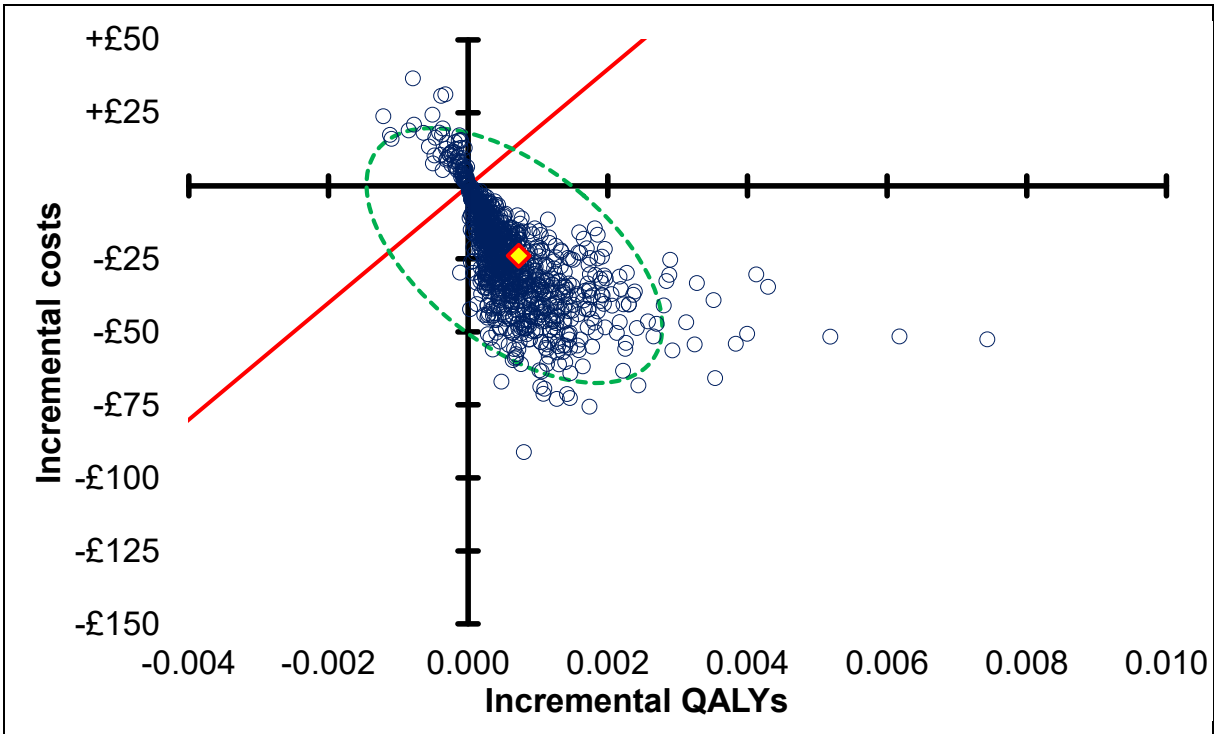
In probabilistic analysis for each base cases of the 4 prices of chlorhexidine + alcohol, chlorhexidine + alcohol was always associated with a probability of at least 83% of being cost-saving. Furthermore, in all probabilistic analyses, the cost-effectiveness acceptability curve shows that aqueous iodine was associated the least probability of being cost-effective at approximately 0%.

Each of the 4 base-case probabilistic analysis scatter plots have the majority of the 5,000 iterations, and the average incremental cost and effect, in the ‘south-east’ quadrant, showing that chlorhexidine + alcohol was a dominant strategy compared with aqueous chlorhexidine.



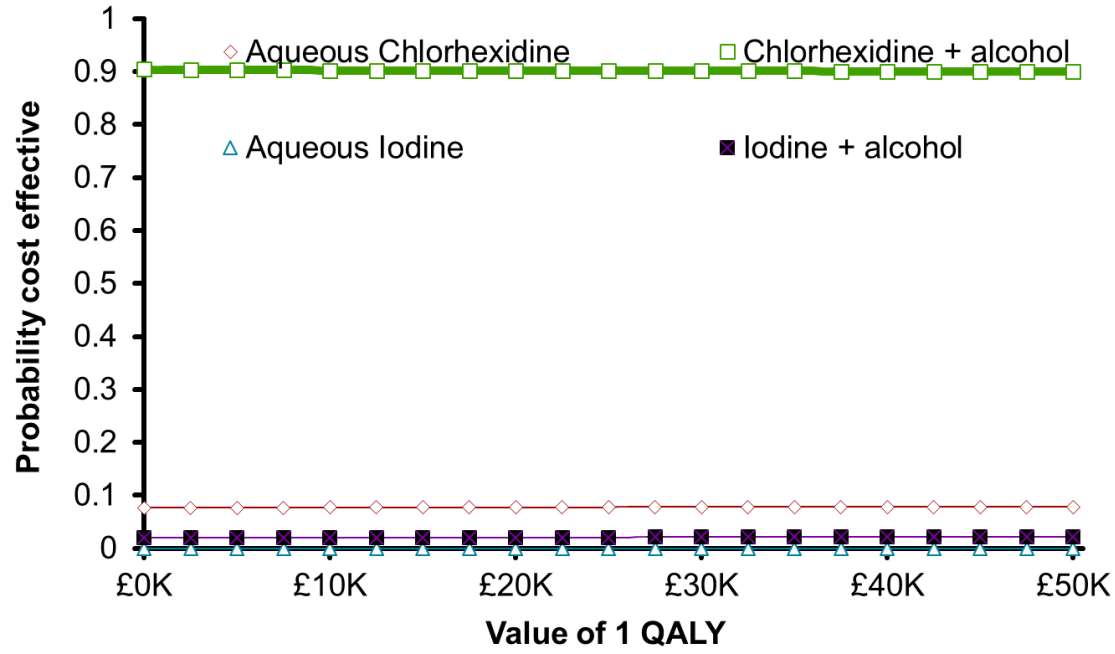
At all values of a QALY, chlorhexidine+alcohol was associated with a 90% probability of being cost effective, whilst aqeous iodine was associated with a 0% probability of being cost-effectiveness.

Figure HE17. Cost-effectiveness acceptability curve for where Chlorhexidine + Alcohol costs = 2% Ecolab



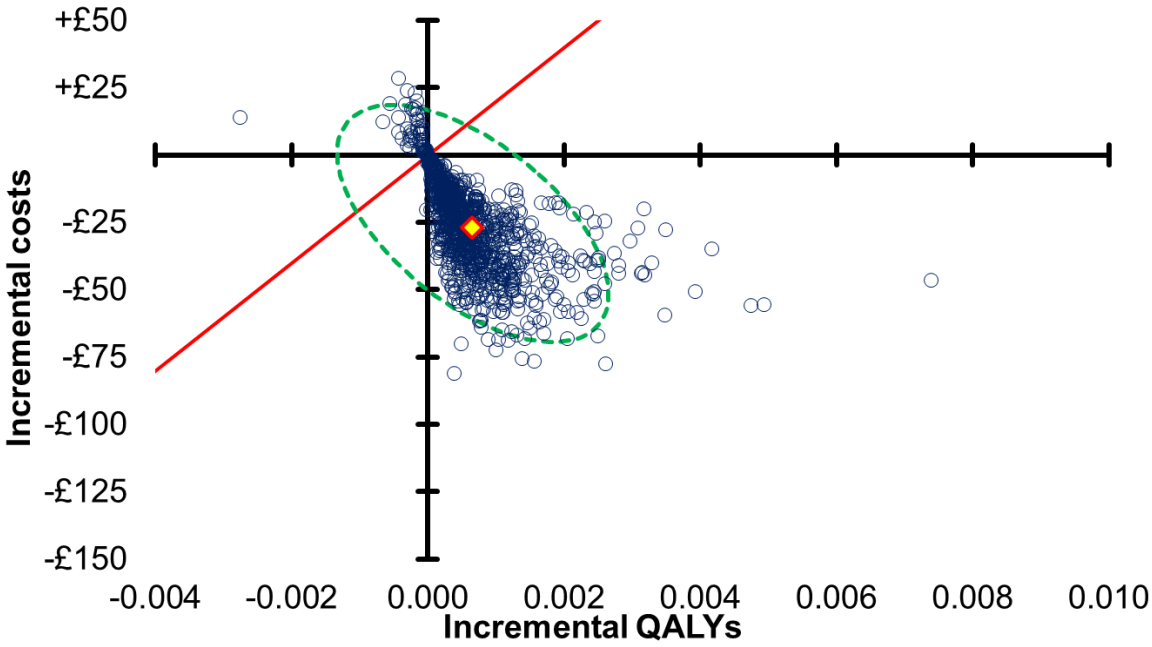
The marker showing the average incremental cost and effects (yellow diamond with the red borders) is in the south east quadrant, showing that Chlorhexidine+alcohol is dominant compared to aqeous chlorhexidine.

Figure HE18. Probabilistic sensitivity analysis comparison of Chlorhexidine + Alcohol vs Chlorhexidine + Aqueous for where Chlorhexidine + Alcohol costs = 2% Ecolab, 5,000 iterations



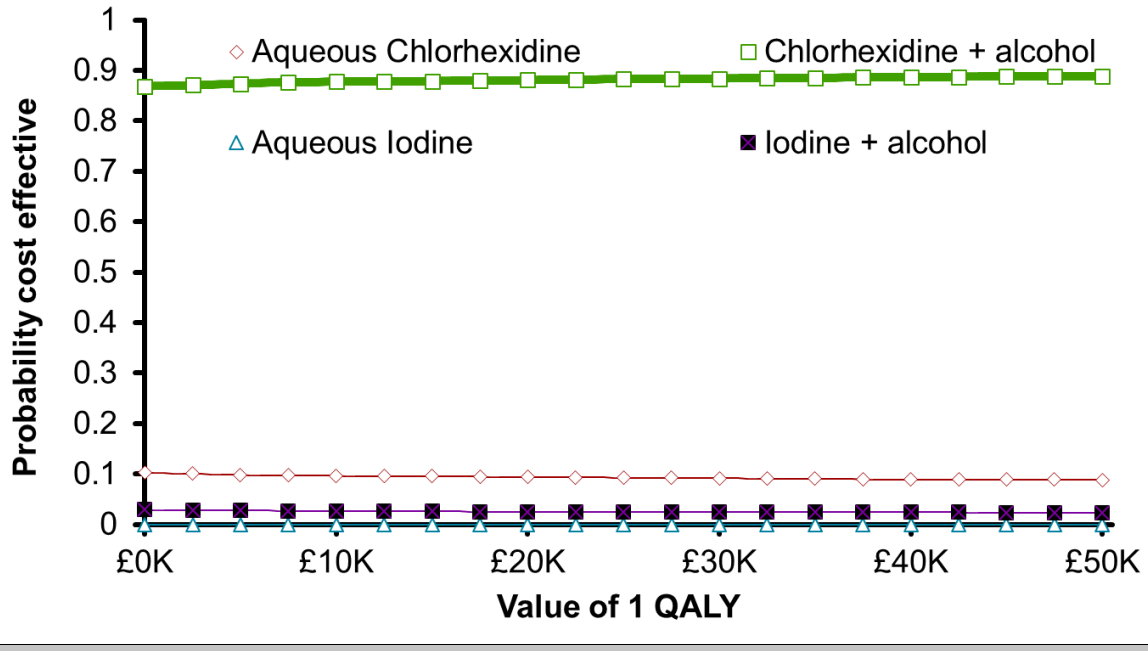
At all values of a QALY, chlorhexidine+alcohol was associated with a 90% probability of being cost effective, whilst aqeous iodine was associated with a 0% probability of being cost-effectiveness.

Figure HE19.Cost-effeciveness acceptability curve for where Chlorhexidine + Alcohol costs = Hydrex



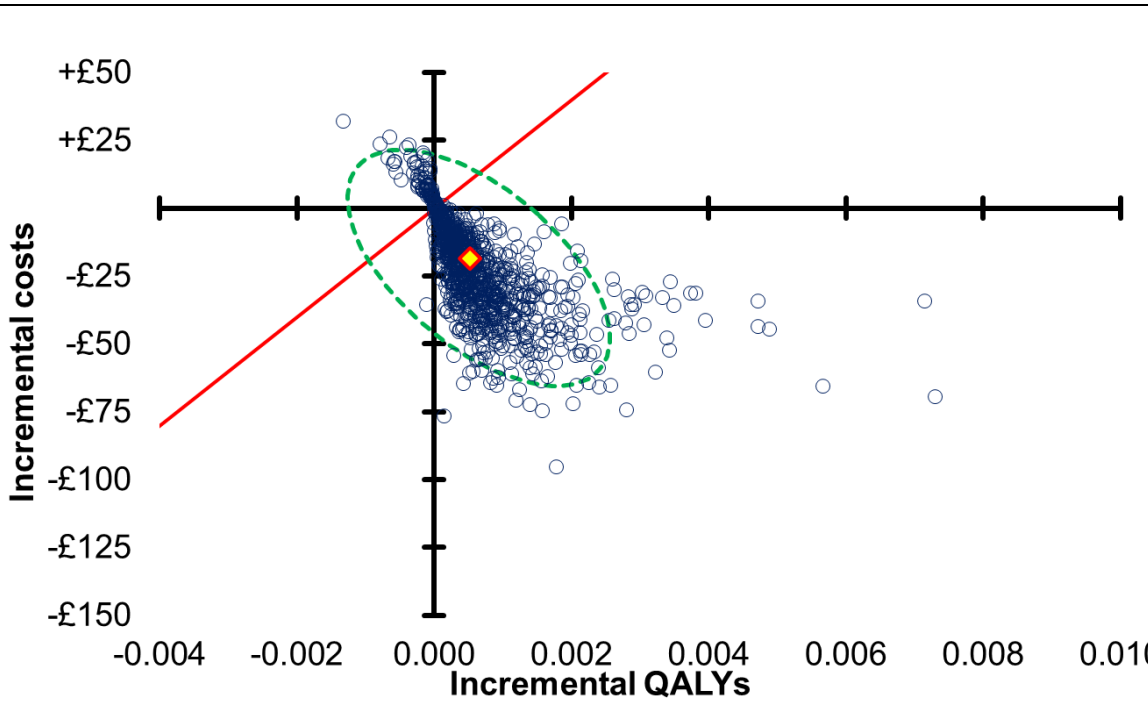
The marker showing the average incremental cost and effects (yellow diamond with the red borders) is in the south east quadrant, showing that Chlorhexidine+alcohol is dominant compared to aqeous chlorhexidine.

Figure HE20. Probabilistic sensitivity analysis comparison of Chlorhexidine + Alcohol vs Chlorhexidine + Aqueous for where Chlorhexidine + Alcohol costs = Hydrex, 5,000 iterations



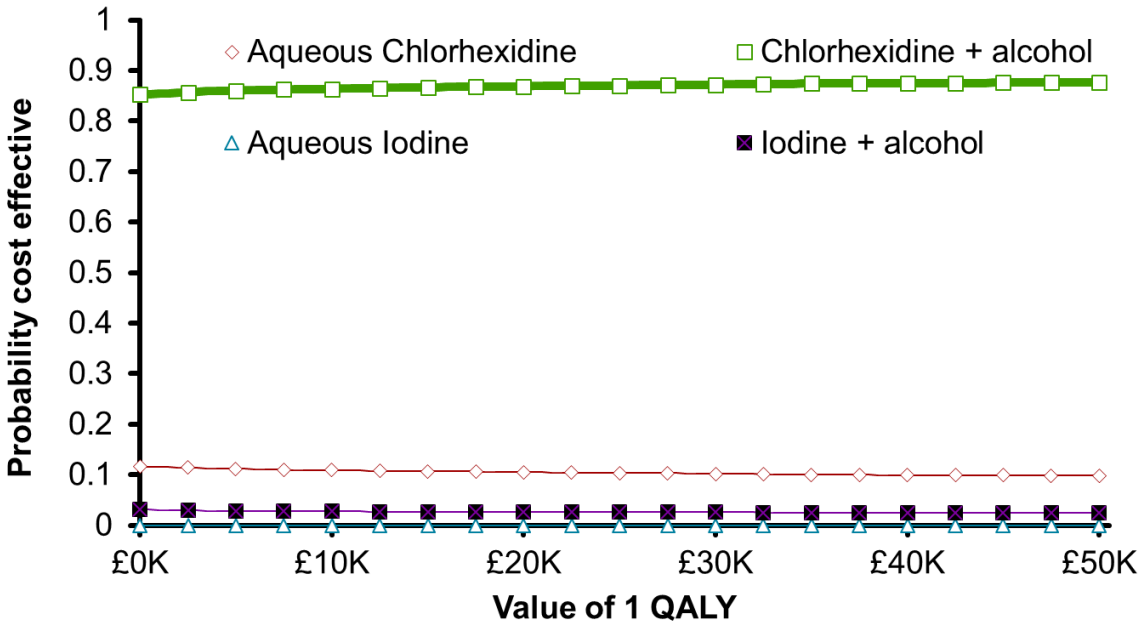
At all values of a QALY, chlorhexidine+alcohol was associated with a 83% probability of being cost effective, whilst aqeous iodine was associated with a 0% probability of being cost-effectiveness.

Figure HE21. Cost-effectiveness acceptability curve for where Chlorhexidine + Alcohol costs = ChloraPrep



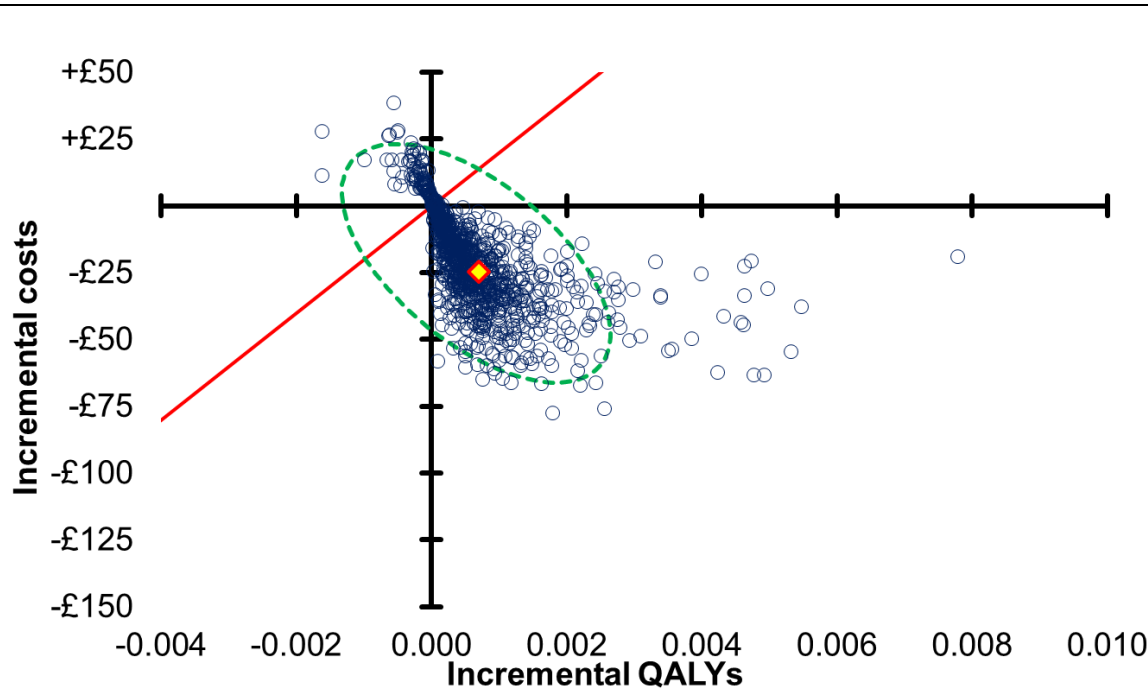
The marker showing the average incremental cost and effects (yellow diamond with the red borders) is in the south east quadrant, showing that Chlorhexidine+alcohol is dominant compared to aqeous chlorhexidine.

Figure HE22. Probabilistic sensitivity analysis comparison of Chlorhexidine + Alcohol vs Chlorhexidine + Aqueous for where Chlorhexidine + Alcohol costs = ChloraPrep, 5,000 iterations



At all values of a QALY, chlorhexidine+alcohol was associated with a 83% probability of being cost effective, whilst aqeous iodine was associated with a 0% probability of being cost-effectiveness.

Figure HE23. Cost-effectiveness acceptability curve for where Chlorhexidine + Alcohol costs = ChloraPrep+Tint



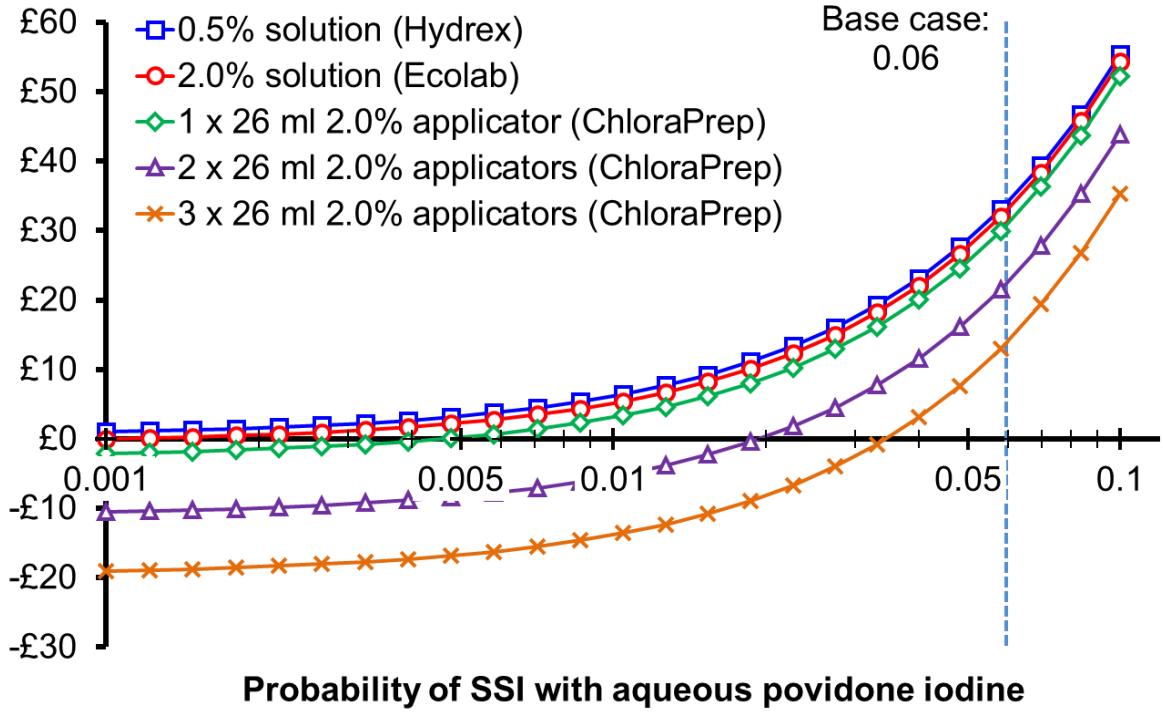
The marker showing the average incremental cost and effects (yellow diamond with the red borders) is in the south east quadrant, showing that Chlorhexidine+alcohol is dominant compared to aqeous chlorhexidine.

Figure HE24. Probabilistic sensitivity analysis comparison of Chlorhexidine + Alcohol vs Chlorhexidine + Aqueous for where Chlorhexidine + Alcohol costs = ChloraPrep+Tint, 5,000 iterations

HE.2.3.4 Baseline SSI

The baseline rate of SSIs used in model was 5.1% – implying that an SSI rate of approximately 6% would have been observed if all operations in Jenks et al.'s (2014) series had used aqueous iodine. This dataset comprises SSIs from 17 different categories of surgery, which are associated with different SSI rates (ranging from 1.0% to 13.0%), different patient demographics (mean age ranging from 51 to 84) and different mortality risks (ranging from 0.0% to 6.2%).

When the baseline risk of SSI alone is altered, chlorhexidine + alcohol provides good value for money at all baseline rates compared with its closest competitor (aqueous chlorhexidine), if the model uses the costs of 0.5% solution (Hydrex) or 2.0% solution (Ecolab). If the costs of 1, 2 or 3 x 2% 26 ml applicators (ChloraPrep) are used, expected baseline SSI risks of 0.5%, 2.0% and 3.5%, respectively, would be required to justify the costs of chlorhexidine + alcohol. See Figure HE25.



Incremental NMB values greater than 0 indicate that a given chlorhexidine + alcohol product would be associated with an ICER better than £20,000 per QALY compared with the next cheapest non-dominated option (aqueous chlorhexidine)

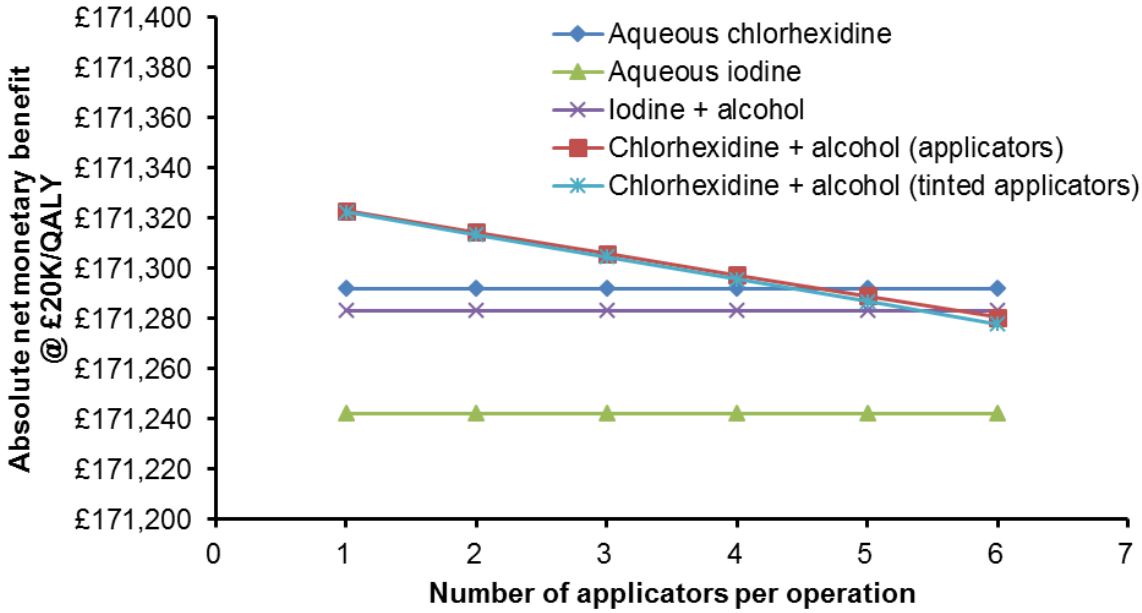
Figure HE25: One-way sensitivity analysis: cost effectiveness of chlorhexidine + alcohol as a function of baseline probability of SSI

HE.2.3.5 Additional sensitivity analyses

The committee requested 2 additional sensitivity analyses that explored uncertainty around the use of chlorhexidine + alcohol applicators. The first examined the number of applicators per operation – see Figure HE26. This analysis shows that, if the number of applicators used per operation is 4 or less, chlorhexidine + alcohol will be associated with an ICER of better than £20,000 / QALY compared with all alternatives. If the number of applicators rises to 5, aqueous chlorhexidine would be preferred and, if as many as 6 applicators per operation were used, chlorhexidine + alcohol would also provide worse value for money than iodine +

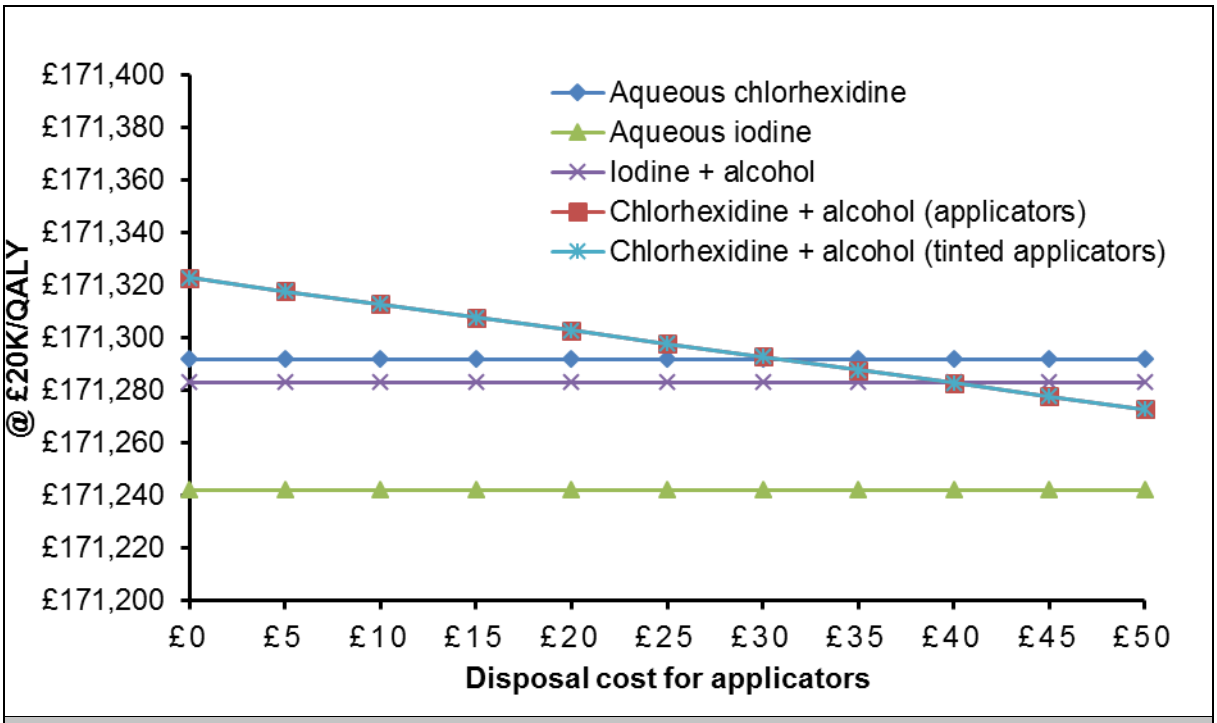
alcohol. The guideline committee advised that these numbers are extremely unlikely; therefore, the cost effectiveness of chlorhexidine + alcohol does not appear to be materially affected by this uncertainty.

The second sensitivity analysis requested by the committee concerns the disposal costs of chlorhexidine + alcohol applicators, which is a source of uncertainty. This analysis (Figure HE27) shows that chlorhexidine + alcohol would be the preferred option unless disposal costs per operation exceed £30, at which point aqueous chlorhexidine would be preferred; if they exceeded £40 per operation, it would also be overtaken by iodine + alcohol. Again, the committee advised that these values are beyond the range of plausible disposal costs; therefore, the results appear robust to this uncertainty.



The option with the highest NMB is associated with the best balance of benefits and costs when QALYs are valued at £20,000 each

Figure HE26: One-way sensitivity analysis: number of 26 ml 2.0% chlorhexidine (ChloraPrep) applicators per operation



The option with the highest NMB is associated with the best balance of benefits and costs when QALYs are valued at £20,000 each

Figure HE27: One-way sensitivity analysis: disposal cost for chlorhexidine applicators (ChloraPrep) per operation

HE.2.4 Discussion

All analyses run for the model found that chlorhexidine + alcohol is the dominant perioperative skin antiseptic strategy, whilst aqueous iodine was the worst performing agent.

As the model was primarily driven by single parameter – the risk of SSI with any given perioperative skin antiseptic preparation – we expected the costs and QALYs in each of the PSAs to be closely correlated, and the spread of the iterations to be similar – and this indeed turned out to be the case. Notably, each of the 4 PSAs comparing chlorhexidine + alcohol at different costs with aqueous chlorhexidine has a very similar distribution, and only shifted slightly when the cost of the strategy is changed.

All OSA comparisons of chlorhexidine + alcohol vs aqueous chlorhexidine showed that the only parameter able to reduce the INMB below £0 was the log odds ratio of alcohol as compared with an aqueous solution, when decreased to its lower 95% credible limit. This is a direct result of the uncertainty in the NMA. For example, in the relevant 'rankograms' (Evidence review B, figure 9), we can seen that chlorhexidine + alcohol has a high probability of being the optimal option, but that probability is less than 95%, as is also evident in the fact that the credible interval for chlorhexidine + alcohol compared with aqueous chlorhexidine crosses 1 (Evidence review B, table 9). As a consequence, the HE model estimates a high probability that chlorhexidine + alcohol provides best value for money, though that probability is less than 95%.

As the model assumes class effects remain constant between all analyses, it will always prefer the cheapest implementation of chlorhexidine + alcohol strategy, which was 2% (Ecolab). However, it is worth to note that the other chlorhexidine + alcohol strategies costs using differing products were very close behind, with ChloraPrep and ChloraPrep+Tint having incremental strategy costs of £2.21 and £2.59 respectively.

HE.2.4.1 Principal findings

- Chlorhexidine + alcohol is the dominant skin antiseptic agent for use prior to any surgical procedure where it is appropriate, whereas aqueous iodine is the least cost-effective option.
- There is significant uncertainty in the cost effectiveness between aqueous chlorhexidine and iodine + alcohol.

HE.2.4.2 Strengths of the analysis

- This is the first analysis of its type to be undertaken in the context of the UK NHS. It benefited from a novel network meta-analysis combining all relevant randomised evidence. The data underpinning absolute SSI calculations were from a well powered source that was directly relevant to the decision problem.
- The analysis is transparent and simple, with relatively few assumptions.

HE.2.4.3 Weaknesses of the analysis

- This analysis only examines skin preparation with a single agent. We did not have any information on double preparation of sites prepared for surgery, the use of a combination of agents, or strategies involving a delay after the initial application, or between multiple applications.
- The model did not consider time required to use each of the skin antiseptic agents, or resultant effects on operating time required – we have no evidence that these systematically differ between approaches but, if they do, it could influence the balance of benefits and costs.
- In simulating different surgical specialities, we accounted for different underlying risks of SSI, amongst other factors. However, our analyses assume that the 4 perioperative skin antiseptic agents have the same relative effect of reducing the incidence of SSI across all settings. It is possible that some approaches are relatively more effective in some settings than others; if so, our model will fail to capture this.
- Similarly, baseline event rates for each subtype of surgery are simulated based on an assumption that similar proportions of antiseptic regimens were used in the Jenks et al. (2014) dataset across each surgical subtype. We did not have granular information for the use perioperative skin antiseptic preparations and associated infection rates for each of the 17 different surgery types considered by the model.

HE.2.4.4 Comparison with other CUAs

We did not identify any other CUAs during our literature search, which means our analysis is the first of its kind for an English NHS context.

HE.2.5 Conclusion

This model found that chlorhexidine + alcohol strategy is the most cost-effective preoperative skin antiseptic in the prevention of surgical site infection.

HE.3 Model parameters

Name	*Value (95%CI)*	*Distribution & parameters*	*Source*
Nasal carriage of Staphylococcus aureus			
UK prevalence of S aureus nasal carriage	25% (21.0, 30.3)	Beta, α=85.252 β=250.386	den Heijer 2013
SSI caused by Staphylococcus aureus			
Proportion SSI caused by S aureus - Jenks 2014	33%	Beta α=4748 β=9552	Jenks et al. 2014
Proportion SSI caused by S aureus - PHE 2017	11%	Beta α=922 β=7460	PHE 2017
Estimating a carrier S aureus SSI incidence odds ratio			
Perl 2002			
No nasal decontamination - whole pop'n	2.4%		Perl 2002
No nasal decontamination - carriers	5.9%		Perl 2002
No nasal decontamination - non-carriers	1.4%		Perl 2002
Kalmeijer 2002			
No nasal decontamination - whole pop'n	2.7%		Kalmeijer 2002
No nasal decontamination - carriers	5.3%		Kalmeijer 2002
No nasal decontamination - non-carriers	1.5%		Kalmeijer 2002
Pooled odds ratio - carriers vs whole pop'n	2.44		
Log(odds) ratio - carriers vs. whole pop'n	0.893	Normal, μ=0.893 σ=0.151	Perl 2002; Kalmeijer 2002
Estimating a non-carrier SSI incidence odds ratio			
Pooled odds ratio - carriers vs non carriers	4.38 (2.584, 6.733)		
Log(odds) ratio - carriers vs non-carriers	1.478 (1.04873, 1.90710)	Normal, μ=1.478 σ=0.219	Perl 2002; Kalmeijer 2002
Estimating a carrier any cause SSI incidence odds ratio			
Perl 2002			
No nasal decontamination - whole pop'n	8.5%		Perl 2002
No nasal decontamination - carriers	11.6%		Perl 2002
No nasal decontamination - non-carriers	7.5%		Perl 2002
Odds ratio - carriers vs whole pop'n	1.42		
Log(odds) ratio - carriers vs. whole pop'n	0.350	Normal, μ=0.350 σ=0.107	Perl 2002
Estimating a non-carrier any cause SSI incidence odds ratio			
Odds ratio - carriers vs non carriers	1.61 (1.19918, 2.16871)		
Log(odds) ratio - carriers vs non-carriers	0.478 (0.18164, 0.77413)	Normal, μ=0.478 σ=0.151	Perl 2002
Perl 2002			
Proportion of SSIs caused by S aureus - carriers	50% (36.60%, 63.40%)	Beta, α=26 β=26	Perl 2002

Proportion of SSIs caused by S aureus - non-carriers	18% (11.37%, 25.43%)	Beta, α=20 β=92	Perl 2002
Baseline SSI incidence - carriers of S aureus			
Selected value, carriers: All surgery	4.1%		Calculated value
ln(odds)	-3.1637		Calculated value
Baseline SSI incidence - non-carriers			
Selected value, non-carriers: All surgery	1.0%		Calculated
ln(odds)	-4.6416		Calculated
Screening			
Nasal culture / screen sensitivity	0.682 (68.2% 98.0%)		CG74; Ritchie 2007; Nsira 2006; Stoakes 2006
Nasal culture / screen specificity	0.945 (94.5% 99.8%)		CG74; Ritchie 2007; Nsira 2006; Stoakes 2006
Pr(T+, and carrier)	0.173228		
Pr(T+ and non-carrier)	0.04103		
Pr(T- and non-carrier)	0.70497		
Pr(T- and carrier)	0.080772		
Efficacy - meta-analysis of RCTs – outcome – Aureus SSI			
Mupirocin + SC vs. Standard care			
All concentrations & durations: mup ln(OR) - FE	-0.762	Normal, (μ=-0.762, σ=0.207)	Bode 2010; Kalmeijer 2002; Konvalinka 2006; Perl 2002; Tai 2013
All concentrations & durations: mup ln(OR) - RE	-0.759	Normal, (μ=-0.759, σ=0.230)	Bode 2010; Kalmeijer 2002; Konvalinka 2006; Perl 2002; Tai 2013
mup OR	0.467 (0.3113 0.7002)		Calculated value
ln(odds) SSI with treatment	-3.93		Calculated value
Scenario analysis - exclude Tai 2013 (Mohs surgery)			
All concentrations & durations: mup ln(OR) - FE	-0.717	Normal, (μ=-0.717, σ=0.220)	Bode 2010; Kalmeijer 2002; Konvalinka 2006; Perl 2002
All concentrations & durations: mup ln(OR) - RE	-0.693	Normal, (μ=-0.693, σ=0.283)	Bode 2010; Kalmeijer 2002; Konvalinka 2006; Perl 2002
mup OR	0.488 (0.3172 0.7518)		Calculated value
ln(odds) SSI with treatment	-3.88		Calculated value
Scenario analysis - exclude Kalmeijer 2002 (no mention of control CH)			
All concentrations & durations: mup ln(OR) - FE	-0.750	Normal, (μ=-0.750, σ=0.213)	Bode 2010; Konvalinka 2006; Perl 2002; Tai 2013
All concentrations & durations: mup ln(OR) - RE	-0.734	Normal, (μ=-0.734, σ=0.278)	Bode 2010; Konvalinka 2006; Perl 2002; Tai 2013
mup OR	0.473 (0.3111 0.7175)		Calculated value
ln(odds) SSI with treatment	-3.91		Calculated value

Scenario analysis - exclude Kalmeijer 2002 and Tai 2013			
All concentrations & durations: mup ln(OR) - FE	-0.700	Normal, (μ=-0.700, σ=0.228)	Bode 2010; Konvalinka 2006; Perl 2002
All concentrations & durations: mup ln(OR) - RE	-0.638	Normal, (μ=-0.638, σ=0.354)	Bode 2010; Konvalinka 2006; Perl 2002
mup OR	0.497 (0.3177 0.7762)		Calculated value
ln(odds) SSI with treatment	-3.91		Calculated value
Treatment effects in whole population cohorts			
Outcome: S aureus deep SSI			
Mupirocin vs. Povidone iodine			
Baseline prob - povidone iodine	0.12%		Phillips 2015
ln(odds)	-6.7346		Calculated value
2% for 5 days: mup ln(OR)	1.599	Normal, μ=1.599 σ=1.097	Phillips 2015
mup OR	4.95		Calculated value
ln(odds) SSI with mup	-5.14		
Prob of SSI with mup	0.58%		
Treatment effects in non-carriers			
Outcome: S aureus SSI			
Mupirocin vs. placebo/no nasal decontamination			
All concentrations & durations: mup ln(OR)	0.258	Normal, μ=0.258 σ=0.280	Kalmeijer 2002; Perl 2002
mup OR	1.29 (0.748, 2.238)		Calculated value
SSI mortality			
Mortality with SSI - value used	1.9%		Calculated value
Mortality without SSI - value used	1.3%		Calculated value
Coello et al. 2005 (used when SSI has excess mortality risk)			
Adjusted mortality OR: SSI vs. no SSI	1.5	Lognormal μ=0.095 σ=0.505	Coello 2005 (used in CG74)
Limb amputation	1.1	Lognormal μ=0.336 σ=0.269	Coello 2005 (used in CG74)
Vascular	1.4	Lognormal μ=-0.117 σ=0.216	Coello 2005 (used in CG74)
Large bowel	0.9	Lognormal μ=0.336 σ=0.828	Coello 2005 (used in CG74)
Small bowel	1.4	Lognormal μ=-0.041 σ=0.312	Coello 2005 (used in CG74)
CABG	1.0	Lognormal μ=0.470 σ=0.438	Coello 2005 (used in CG74)
Reduction of long bone fracture	1.6	Lognormal μ=0.588 σ=0.186	Coello 2005 (used in CG74)
Hip prosthesis	1.8	Lognormal μ=0.405 σ=1.025	Coello 2005 (used in CG74)
Knee prosthesis	1.5	Lognormal μ=0.095 σ=0.505	Coello 2005 (used in CG74)
Probability SSI (PHE data - consistent with baseline mortality data source)			
Probability SSI (PHE data - consistent with baseline mortality data source)	1.3%		
Overall mortality odds for selected surgery	1.3%		
Mortality odds - no SSI	1.3%		

Mortality odds - SSI	1.9%		
Mortality prob without SSI	1.3%		
Mortality prob with SSI	1.9%		
Surgery-specific general mortality rates (used directly if no SSI excess mortality)			
Overall surgery mortality rate - selected value	1.3%, (0.00%, 0.00%)		Calculated value
All surgery	1.3%, (1.16%, 1.48%)		Calculated value
Abdominal hysterectomy	0.0%		PHE 2017
Bile duct, liver or pancreas	1.6%, (0.70%, 2.90%)	Beta α=8 β=487	PHE 2017
Breast	0.1%, (0.03%, 0.22%)	Beta α=4 β=4067	PHE 2017
Cholecystectomy	0.0%		PHE 2017
CABG	1.8%, (0.66%, 3.45%)	Beta α=6 β=330	PHE 2017
Cardiac (non-CABG)	2.3%, (1.95%, 2.69%)	Beta α=143 β=6062	PHE 2017
Cranial	2.8%, (2.10%, 3.59%)	Beta α=53 β=1841	PHE 2017
Gastric	1.1%, (0.37%, 2.33%)	Beta α=5 β=432	PHE 2017
Hip prosthesis	0.2%, (0.16%, 0.24%)	Beta α=83 β=41641	PHE 2017
Knee prosthesis	0.1%, (0.07%, 0.13%)	Beta α=45 β=44892	PHE 2017
Large bowel	2.6%, (2.14%, 3.09%)	Beta α=110 β=4132	PHE 2017
Limb amputation	2.6%, (1.21%, 4.54%)	Beta α=9 β=335	PHE 2017
Reduction of long bone fracture	2.2%, (1.64%, 2.87%)	Beta α=48 β=2123	PHE 2017
Repair of neck of femur	6.2%, (5.86%, 6.54%)	Beta α=1213 β=18357	PHE 2017
Small bowel	3.5%, (2.53%, 4.70%)	Beta α=39 β=1064	PHE 2017
Spinal	0.2%, (0.10%, 0.31%)	Beta α=13 β=6728	PHE 2017
Vascular	3.5%, (2.55%, 4.54%)	Beta α=45 β=1250	PHE 2017
Life expectancy			
Cohort life expectancy (years)	16.9		Calculated value
Long-term morbidity			
Hazard ratio for increased morbidity in post-surgery cohort	1.0		
Screening for nasal S aureus			
Nasal culture			
Cost of nasal culture - committee	£6.66 (£5.08, £8.24)	Normal μ=6.660 σ=0.806	Guideline committee
Cost of nasal swab administration	£3.32		NICE CG74, PSSRU 2017
PCR test			
Cost of PCR - CG74	£19.40 (£9.70, £29.10)	Triangular min=9.7 mode=19.4 max=29.1	NICE CG74
Cost of administration - CG74	£2.55 (£1.28, £3.83)	Triangular min=1.3 mode=2.6 max=3.8	NICE CG74
Inflation index: 2004-05 to 2016-17	1.301		PSSRU, 2017

PCR at current prices	£25.25		Calculated value
Administration at current prices	£3.32		Calculated value
Nasal decontamination intervention			
Mupirocin ± chlorhexidine wash			
Mupirocin			
Mupirocin 2% nasal ointment	£4.24		NHS Drug Tariff (May 2018) VIIIA
Chlorhexidine			
HibiScrub Plus 4% solution (1x 125ml)	£1.50 (£1.50, £4.25)		BNF 2017; Guideline comment
Povidone iodine			
Videne 7.5%/10% solution (1x 500ml)	£7.67		Calculated value
Administration			
Cost per nurse hour (Band 5)	£37.00		PSSRU 2017
Nurse time for application per day (mins) - mup/ch	4.00 (1.0, 10)		https://clinicaltrials.gov/ct2/show/NCT01313182
Total days:	5.0		
Cost per course (mupirocin +/- chlorhexidine)	£0.00		Calculated value
Nurse time for application per day (mins) - povidone iodine	2.00 (1.0, 10)		https://clinicaltrials.gov/ct2/show/NCT01313182
Total days:	1.0		
Cost per course (povidone iodine)	£0.00		Calculated value
Days in hospital due to SSI - median, 2-yrs			
All surgery, days	10, (9.478, 10.522)	Normal, (μ=10.000, σ=0.266)	Jenks et al., 2014
Cardiac, days	24.06, (21.542, 26.586)	Normal, (μ=24.064, σ=1.287)	Jenks et al., 2014
Vascular, days	12.57, (4.501, 20.633)	Normal, (μ=12.567, σ=4.115)	Jenks et al., 2014
Limb amputation, days	10, (5, 20)	Triangular, (min=5.0, mode=10.0, max=20.0)	Jenks et al., 2014
Hip replacement, days	25.84, (-2.235, 53.907)	Normal, (μ=25.836, σ=14.322)	Jenks et al., 2014
Knee replacement, days	7, (3.5, 14)	Triangular, (min=3.5, mode=7.0, max=14.0)	Jenks et al., 2014
Reduction long bone fracture, days	12.93, (1.407, 24.456)	Normal, (μ=12.932, σ=5.880)	Jenks et al., 2014
Repair neck of femur, days	19, (9.5, 38)	Triangular, (min=9.5, mode=19.0, max=38.0)	Jenks et al., 2014
Cranial, days	5.47, (-5.962, 16.896)	Normal, (μ=5.467, σ=5.831)	Jenks et al., 2014
Spinal, days	15.58, (5.051, 26.104)	Normal, (μ=15.577, σ=5.371)	Jenks et al., 2014
Abdominal hysterectomy, days	14, (7, 28)	Triangular, (min=7.0, mode=14.0, max=28.0)	Jenks et al., 2014
Caesarean section, days	4.36, (2.817, 5.899)	Normal, (μ=4.358, σ=0.786)	Jenks et al., 2014
Breast, days	2.64, (1.341, 3.93)	Normal, (μ=2.636, σ=0.660)	Jenks et al., 2014

Bile duct/liver/pancreas, days	13.48, (2.819, 24.141)	Normal, (μ=13.480, σ=5.439)	Jenks et al., 2014
Cholecystectomy, days	8, (4, 16)	Triangular, (min=4.0, mode=8.0, max=16.0)	Jenks et al., 2014
Gastric, days	29, (14.5, 58)	Triangular, (min=14.5, mode=29.0, max=58.0)	Jenks et al., 2014
Large bowel, days	9.58, (7.944, 11.226)	Normal, (μ=9.585, σ=0.837)	Jenks et al., 2014
Small bowel, days	14.9, (6.934, 22.866)	Normal, (μ=14.900, σ=4.064)	Jenks et al., 2014
Multiple & intra-abdominal, days	9.88, (3.586, 16.174)	Normal, (μ=9.880, σ=3.211)	Jenks et al., 2014
Multiple & other, days	20, (10, 40)	Triangular, (min=10.0, mode=20.0, max=40.0)	Jenks et al., 2014
Additional cost due to SSI - median, 2-years			
All surgery, cost	£5,542 (£1,563)	Gamma α=3546.908 β=1.562	Jenks et al., 2014
Cardiac, cost	£11,679(£5,275)	Gamma α=210.768 β=55.411	Jenks et al., 2014
Vascular, cost	£3,760 (£8,357)	Gamma α=2.429 β=1547.876	Jenks et al., 2014
Limb amputation, cost	£6,799	Triangular min=3399.5 mode=6799.0 max=13598.0	Jenks et al., 2014
Hip replacement, cost	£7,363 (£3,897)	Gamma α=3.088 β=2384.375	Jenks et al., 2014
Knee replacement, cost	£2,356	Triangular min=1178.0 mode=2356.0 max=4712.0	Jenks et al., 2014
Reduction long bone fracture, cost	£5,773 (£9,282)	Gamma α=7.348 β=785.590	Jenks et al., 2014
Repair neck of femur, cost	£12,104	Triangular min=6052.0 mode=12104.0 max=24208.0	Jenks et al., 2014
Cranial, cost	£8,237 (£7,749)	Gamma α=1.938 β=4249.414	Jenks et al., 2014
Spinal, cost	£9,721 (£12,345)	Gamma α=6.820 β=1425.272	Jenks et al., 2014
Abdominal hysterectomy, cost	£5,983	Triangular min=2991.5 mode=5983.0 max=11966.0	Jenks et al., 2014
Caesarean section, cost	£3,131 (£3,153)	Gamma α=24.657 β=127.000	Jenks et al., 2014
Breast, cost	£2,286 (£2,418)	Gamma α=12.518 β=182.632	Jenks et al., 2014
Bile duct/liver/pancreas, cost	£5,946 (£2,349)	Gamma α=2.319 β=2564.466	Jenks et al., 2014
Cholecystectomy, cost	£6,236	Triangular min=3118.0 mode=6236.0 max=12472.0	Jenks et al., 2014
Gastric, cost	£21,493	Triangular min=10746.5 mode=21493.0 max=42986.0	Jenks et al., 2014
Large bowel, cost	£5,518 (£2,654)	Gamma α=229.054 β=24.089	Jenks et al., 2014

Small bowel, cost	£4,905 (£7,866)	Gamma α=6.221 β=788.450	Jenks et al., 2014
Multiple & intra-abdominal, cost	£3,511 (£11,834)	Gamma α=1.761 β=1994.301	Jenks et al., 2014
Multiple & other, cost	£9,696	Triangular min=4848.0 mode=9696.0 max=19392.0	Jenks et al., 2014
Infection unit cost per bed day			
Infection unit cost per bed day	£312.29 (£236.50, £368.16)		Calculated value
EL_XS			
WH07A: Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 2+	£311.43 (£306.57, £381.32)	Gamma α=379.051 β=0.822, n = 178	NHS Ref Costs 2016-17
WH07B: Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 0-1	£332.68 (£190.67, £365.00)	Gamma α=205.445 β=1.619, n = 683	NHS Ref Costs 2016-17
WH07C: Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+	£361.32 (£257.97, £462.68)	Gamma α=79.367 β=4.552, n = 167	NHS Ref Costs 2016-17
WH07D: Infections or Other Complications of Procedures, with Single Intervention, with CC Score 0-1	£343.69 (£276.20, £462.46)	Gamma α=303.599 β=1.132, n = 567	NHS Ref Costs 2016-17
WH07E: Infections or Other Complications of Procedures, without Interventions, with CC Score 4+	£322.29 (£300.00, £323.26)	Gamma α=1746.833 β=0.184, n = 132	NHS Ref Costs 2016-17
WH07F: Infections or Other Complications of Procedures, without Interventions, with CC Score 2-3	£268.01 (£121.95, £335.46)	Gamma α=94.619 β=2.832, n = 532	NHS Ref Costs 2016-17
WH07G: Infections or Other Complications of Procedures, without Interventions, with CC Score 0-1	£378.93 (£254.77, £436.82)	Gamma α=1584.656 β=0.239, n = 1,787	NHS Ref Costs 2016-17
NEL_XS			
WH07A: Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 2+	£303.04 (£195.56, £351.13)	Gamma α=400.498 β=0.757, n = 1,842	NHS Ref Costs 2016-17
WH07B: Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 0-1	£337.61 (£268.18, £412.09)	Gamma α=1242.025 β=0.272, n = 2,610	NHS Ref Costs 2016-17
WH07C: Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+	£284.61 (£218.57, £341.35)	Gamma α=713.781 β=0.399, n = 1,275	NHS Ref Costs 2016-17
WH07D: Infections or Other Complications of Procedures, with Single Intervention, with CC Score 0-1	£286.53 (£215.51, £356.49)	Gamma α=1977.025 β=0.145, n = 3,014	NHS Ref Costs 2016-17
WH07E: Infections or Other Complications of Procedures, without Interventions, with CC Score 4+	£311.69 (£259.71, £378.61)	Gamma α=400.160 β=0.779, n = 554	NHS Ref Costs 2016-17
WH07F: Infections or Other Complications of Procedures, without Interventions, with CC Score 2-3	£294.94 (£205.38, £374.03)	Gamma α=1491.637 β=0.198, n = 3963	NHS Ref Costs 2016-17
WH07G: Infections or Other Complications of Procedures, without Interventions, with CC Score 0-1	£312.05 (£249.70, £354.31)	Gamma α=17504.182 β=0.018, n = 15,300	NHS Ref Costs 2016-17
Long-term morbidity			
HRQL loss due to increased morbidity in post-surgery cohort	0.0		
Baseline			

Baseline utility weight	0.780		
Quality-adjusted life expectancy			
Discounted total QALE (general population)	9.056		ONS 2017; Kind 1999
Total QALYs (QALE minus surgery-SSI loss, for survivors only)			
No SSI	8.924		Calculated value
SSI	8.865		Calculated value
HRQL loss associated with SSI			
EQ-5D utility weights			
EQ-5D at baseline - no SSI	0.762 (0.73607, 0.78701)	Beta α=816.950 β=255.163	Gheorghe, A., 2014
EQ-5D at baseline - SSI	0.718 (0.67187, 0.76196)	Beta α=274.098 β=107.654	
EQ-5D at 7 days - no SSI	0.514 (0.48458, 0.54337)	Beta α=570.149 β=539.091	
EQ-5D at 7 days - SSI	0.464 (0.40937, 0.51906)	Beta α=146.728 β=169.496	
EQ-5D at 30 days - no SSI	0.714 (0.68819, 0.73914)	Beta α=862.018 β=345.290	
EQ-5D at 30 days - SSI	0.594 (0.54855, 0.63867)		
Utility loss multipliers			
Utility multiplier at 7 days - no SSI	67% (63.6%, 71.3%)		Calculated value
Utility multiplier at 7 days - SSI	65% (57.0%, 72.3%)		Calculated value
Utility multiplier at 30 days - no SSI	94% (90.3%, 97.0%)		Calculated value
Utility multiplier at 30 days - SSI	83% (76.4%, 89.0%)		Calculated value
Resulting utility weights			
Utility at 7 days - no SSI	0.526 (0.496 , 0.556)		Calculated value
Utility at 7 days - SSI	0.504 (0.445 , 0.564)		Calculated value
Utility at 30 days - no SSI	0.731 (0.704 , 0.757)		Calculated value
Utility at 30 days - SSI	0.645 (0.596 , 0.694)		Calculated value
Additional time required to recover to baseline HRQL			
--Current setting: Extended HRQL recovery period--			
Additional recovery time: linear recovery per day			
No SSI - recovery per day trend	1.1%		Calculated value
SSI - recovery per day trend	0.8%		Calculated value
No SSI - additional days to full recovery	5.5 (2.629 ,		Calculated value
SSI - additional days to full recovery	21.9 (14.036 ,		Calculated value
Selected overall utility duration, No SSI, days	36 (32.629 , 38.488)		Calculated value
Selected overall utility duration, SSI, days	52 (44.036, 59.979)		Calculated value
Perioperative QALYs			
No surgery (general population)	0.111		Calculated value

No SSI	0.096		Calculated value
SSI	0.089		Calculated value
Perioperative QALY loss vs. general population			
No SSI	0.015		Calculated value
SSI	0.022		Calculated value
Relative effects for antiseptic model			
Multivariate normal sampling			
Lumped			
Ln(OR) -v- aqueous iodine			
Aqueous iodine	0		NMA
Chlorhexidine in alcohol	-0.407 (-0.613 -0.202)		NMA
Povidone Iodine in alcohol	-0.166 (-0.469 0.137)		NMA
Aqueous Chlorhexidine	-0.175 (-0.638 0.287)		NMA
OR -v- aqueous iodine			
Aqueous iodine	1		Calculated
Chlorhexidine in alcohol	0.665341073		Calculated
Povidone Iodine in alcohol	0.84703963		Calculated
Aqueous Chlorhexidine	0.839063822		Calculated
Meta-regression			
Ln(OR) s			
Alcohol -v- aqueous	-0.186 (-0.446 0.073)		NMA
Chlorhexidine -v- iodine	-0.228 (-0.449 -0.008)		NMA
Ln(OR) -v- aqueous iodine			
Aqueous iodine	0		Calculated
Chlorhexidine in alcohol	-0.414661541		Calculated
Povidone Iodine in alcohol	-0.186311973		Calculated
Aqueous Chlorhexidine	-0.228349568		Calculated
OR -v- aqueous iodine			
Aqueous iodine	1		Calculated
Chlorhexidine in alcohol	0.660563817		Calculated
Povidone Iodine in alcohol	0.830014613		Calculated
Aqueous Chlorhexidine	0.795846009		Calculated
Infection probabilities			
Ln(odds)			
Aqueous iodine	-2.7590		Calculated
Chlorhexidine in alcohol	-3.1737		Calculated
Povidone Iodine in alcohol	-2.9453		Calculated
Aqueous Chlorhexidine	-2.9873		Calculated
Probability			
Aqueous iodine	0.0596		Calculated
Chlorhexidine in alcohol	0.0402		Calculated
Povidone Iodine in alcohol	0.0500		Calculated
Aqueous Chlorhexidine	0.0480		Calculated

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