National Institute for Health and Care Excellence

Draft

Neonatal infection: antibiotics for prevention and treatment

[F] Evidence review for antibiotic-impregnated catheters for reducing late-onset neonatal infection

NICE guideline <number>

Evidence reviews underpinning recommendation 1.5.1 and research recommendations in the NICE guideline

December 2020

Draft for Consultation

These evidence reviews were developed by NICE Guideline Updates Team

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ISBN:

Contents

Antibiotic-impregnated intravascular catheters for reducing the risk of late-onset neonatal infection 6

1.1 Review question 6

What is the clinical and cost effectiveness of intravascular catheters impregnated with antibiotics in reducing the risk of the baby developing late-onset neonatal infection? 6

1.1.1 Introduction 6

1.1.2 Summary of the protocol 6

Table 1 PICO table 6

1.1.3 Methods and process 7

1.1.4 Effectiveness evidence 7

1.1.5 Summary of studies included in the effectiveness evidence 8

1.1.6 Summary of the effectiveness evidence 9

1.1.7 Economic evidence 10

1.1.8 Summary of included economic evidence 11

Summary of studies included in the economic evidence review 11

1.1.9 Economic model 11

1.1.10 The committee's discussion and interpretation of the evidence 11

1.1.11 Recommendations supported by this evidence review 14

1.1.12 References – included studies 15

Appendices 16

Appendix A – Review protocols 16

Appendix B – Literature search strategies 29

Clinical search literature search strategy 29

Health Economics literature search strategy 40

Appendix C – Effectiveness evidence study selection 61

Appendix D – Effectiveness evidence 62

Domain 1: Bias arising from the randomisation process 64

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) 64

Domain 3. Bias due to missing outcome data 64

Domain 4. Bias in measurement of the outcome 64

Domain 5. Bias in selection of the reported result 64

Overall bias and Directness 64

Domain 1: Bias arising from the randomisation process 71

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) 71

Domain 3. Bias due to missing outcome data 71

Domain 4. Bias in measurement of the outcome 71

Domain 5. Bias in selection of the reported result 71
Overall bias and Directness 71
Appendix E – Forest plots 72
Appendix F – GRADE tables 75
Appendix G – Economic evidence study selection 78
Appendix H – Economic evidence tables 79
Appendix I – Health economic model 81
Appendix J – Excluded studies 82
Clinical studies 82
Economic studies 83
Appendix K – Research recommendations – full details 84
K.1.1 Research recommendation 84
K.1.2 Why this is important 84
K.1.3 Rationale for research recommendation 84
K.1.4 Modified PICO table 85
K.1.1 Research recommendation 85
K.1.2 Why this is important 85
K.1.3 Rationale for research recommendation 86
K.1.4 Modified PICO table 87

Antibiotic-impregnated intravascular catheters for reducing the risk of late-onset neonatal infection

1.1 Review question

What is the clinical and cost effectiveness of intravascular catheters impregnated with antibiotics in reducing the risk of the baby developing late-onset neonatal infection?

1.1.1 Introduction

Neonatal infection is a significant cause of mortality and morbidity in newborn babies. It can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths. Late-onset neonatal infection occurs more than 72 hours after birth, is present in 7 of every 1000 newborn babies and is responsible for 61 of every 1000 neonatal admissions. Coagulase-negative staphylococci, Enterobacteriaceae and Staphylococcus aureus are the most common organisms identified.

Intravascular catheters are commonly used in neonatal care for the delivery of fluids and medication to the baby. However, catheters are also associated with the development of bloodstream infection. The use of antimicrobial-impregnated intravascular catheters may therefore help to reduce the risk of late-onset neonatal infection. The aim of this review is to establish the clinical and cost-effectiveness of antimicrobial-impregnated intravascular catheters in comparison to standard catheters for neonatal care in reducing the risk of late-onset neonatal infection.

1.1.2 Summary of the protocol

Table 1 PICO table

Population	Term babies up to 28 days of age and preterm babies up to 28 days corrected gestational age who have had or are having an intravascular catheter inserted
Interventions	Intravascular catheter (PICC lines or umbilical venous catheters) impregnated with antibiotics, including: • Rifampicin (with or without miconazole) • Minocycline-rifampicin
Comparator	• Head-to-head comparison between types of impregnated catheter • Non-impregnated PICC lines or umbilical venous catheters
Outcomes	• culture-proven infection from sample taken between 72 hours (where available) and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection • suspected bloodstream infection (in neonate) based on clinical symptoms. Measured between 72 hours (where available) and 28 days of age (term babies) or 28 days corrected gestational

	age (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection • duration of antibiotic exposure (neonate) • neonatal mortality • health-related quality of life of the baby, measured using a validated tool • hospital length of stay • psychological distress in baby's family as measured using a validated scale (e.g. parental stressor scale NICU; modified Rutter Malaise Inventory) • antimicrobial resistance (culture-proven or from the intravascular catheter)

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A. For full methods for this review see the methods document.

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

Randomised controlled trials (RCTs) and systematic reviews of RCTs were considered. The review protocol specified that, where possible, subgroup analyses would be conducted for gestational age of the baby (preterm vs term) and for babies who had been admitted to hospital from home. The review also examined which class or classes of antimicrobial were used to impregnate the catheter. This was highlighted to the committee and in GRADE tables and forest plots.

This review did not use the GRADE imprecision parameter as part of the quality assessment of outcome measures. Where the interpretation of the effect is stated in the quality assessment table (Table 3), an outcome was reported as 'could not differentiate between trial arms' when the confidence intervals crossed the line of no effect. The imprecision associated with a particular outcome and more detailed discussions of the effects are described in the committee's discussion of the evidence.

Note that although the inclusion criteria for the review was intravascular catheters impregnated with antibiotics, we took a broad definition of this as including any antimicrobial substance active against bacteria.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

The initial search returned a total of 389 results. Of these, 13 were identified as potential included studies and full text articles were ordered and reviewed against the inclusion criteria. Two RCTs met the inclusion criteria and were included within the review.

The search was re-run in July 2020 to identify any studies which had been published since the date of the original search. This returned a total of 95 results of which 1 was identified as a possible included study. After full text review, 1 RCT met the inclusion criteria. In total there were therefore 3 studies (all RCTs) which met the inclusion criteria for this review.

See Appendix D for evidence tables of included studies.

1.1.4.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2 Summary of included clinical studies

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
Bertini 2013 (n=98)	• RCT • Mean follow-up time 6.4 (±4.3) days	Infants with a gestational age over 30 weeks who required an umbilical venous catheter (UVC) in the first week of life for parenteral nutrition and/or therapy	AgION impregnated catheter *(AgION silver zeolite-impregnated polyurethane catheter)*	Non-impregnated catheter *(Polyurethane catheter)*	• Culture-proven late-onset neonatal infection *(from blood sample that was positive for the same organism found to colonize the UVC tip)* • Suspected late-onset neonatal infection *(one positive UVC tip culture and negative or not concordant positive blood culture drawn from the UVC, clinical manifestations of infection with a central line)* • Neonatal length of stay *(days)* • Neonatal mortality
Gilbert 2019 (PREVAIL trial) n=861	• RCT • Infection outcome follow-up: 48 hours after PICC removal	Babies requiring a narrow-gauge peripherally inserted central venous catheter (CVC)	Antimicrobial impregnated PICC *(PICC impregnated with miconazole*	Standard PICC *(non-impregnated PICC)*	• Culture-proven late-onset neonatal infection *(Microbiological culture of a bacteria or fungus from*

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
	or after last unsuccessful PICC insertion • Secondary outcome follow-up: Until discharge, death or 6 months after randomisation (whichever occurred first)		*and rifampicin)*		*the blood or CSF)* • Neonatal mortality *(before discharge and 6 months from randomisation)* • Antimicrobial resistance *(from blood or CSF culture and from PICC tip culture)*
Klemme 2020 n=77	• RCT • 21 day follow-up	All preterm and term infants who had a clinical indication for a percutaneous inserted central catheter (PICC)	Antimicrobial impregnated PICC *(PICC impregnated with miconazole and rifampicin)*	Standard PICC *(non-impregnated PICC)*	• Culture-proven late-onset neonatal infection *(0 cases in each arm so results not reported in meta-analysis)*

1 See appendix D for full evidence tables.

2 ### 1.1.6 Summary of the effectiveness evidence

Comparison	No. studies	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Miconazole and rifampicin vs standard PICC					
Late-onset neonatal infection: Culture-proven or suspected	1 (Gilbert 2019)	861	RR 1.05 (0.71 to 1.55)	High	Could not differentiate
Late-onset neonatal infection: Culture-proven infection	1 (Klemme 2020)	77	RD 0.00 (-0.05 to 0.05)	Moderate	Could not differentiate
Neonatal mortality (before hospital discharge)	1 (Gilbert 2019)	861	RR 1.09 (0.70 to 1.72)	High	Could not differentiate
Neonatal mortality (6-month follow up)	1 (Gilbert 2019)	861	RR 1.03 (0.66 to 1.61)	High	Could not differentiate

Comparison	No. studies	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Antimicrobial resistance (blood or CSF culture)	1 (Gilbert 2019)	861	RR 0.57 (0.17 to 1.94)	High	Could not differentiate
Antimicrobial resistance (PICC tip culture)	1 (Gilbert 2019)	861	RR 3.51 (1.16 to 10.57)	High	Favours standard catheter
Silver zeolite vs standard UVC					
Late-onset neonatal infection (culture-proven or suspected) (Silver zeolite vs standard UVC)	1 (Bertini 2013)	86	RR 0.18 (0.04 to 0.78)	Low	Favours silver zeolite
Duration of neonatal antibiotic exposure (days)	1 (Bertini 2013)	86	MD -0.10 (-0.44 to 0.24)	Low	Could not differentiate
Neonatal mortality (before hospital discharge)	1 (Bertini 2013)	86	RR 0.73 (0.21 to 2.53)	Low	Could not differentiate
Neonatal length of stay (days)	1 (Bertini 2013)	86	MD -15.00 (-29.41 to -0.59)	Low	Favours silver zeolite

See appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B). This search retrieved 4,398 studies. Based on title and abstract screening, all of the studies could confidently be excluded for this question.

The search was re-run in July 2020 to identify any studies which had been published since the date of the original search. This returned a total of 577 results. Based on title and abstract screening, 1 study was suspected to be relevant and was ultimately included. Therefore, in total there was one study which met the inclusion criteria for this review.

1.1.7.2 Excluded studies

See appendix J for excluded studies.

1.1.8 Summary of included economic evidence

Summary of studies included in the economic evidence review

Applicability & limitations	Other comments	Intervention	Absolute		Incremental			Uncertainty
			Cost (£)	QALYs	Cost (£)	QALYs	Net health benefit at £20,000/ QALY	
Grosso et al (2020)								
Partially applicable (appendix H) with potentially serious limitations (appendix H)	**Approach to analysis:** Excel based model to estimate the direct cost and effectiveness (QALYs) associated with late onset infection (LOI) for a lifetime horizon. **LOI related complications considered:** No neurodevelopmental impairment (NDI), mild NDI, moderate NDI, severe NDI **Perspective:** UK NHS	**Gestational age (weeks) 23-27**						**Deterministic:** Sensitivity analysis showed that the base case results of the model were robust to all parameters except the relative risk of infection with AM-PICCs and the effect of LOI on the risk of death. If AM-PICCs successfully reduce the risk of LOI they would have a positive net health benefit. **Probabilistic:** No probabilistic sensitivity analysis was conducted.
		Standard non-impregnated PICCs (S-PICCs)	127,128	16.49				
		Antimicrobial impregnated PICCs (AM-PICCs)	127,183	16.48	55	-0.01	-0.01	
		Gestational age (weeks) 28-32						
		Standard non-impregnated PICCs (S-PICCs)	83,533	21.46				
		Antimicrobial impregnated PICCs (AM-PICCs)	83,588	21.46	55	0.00	-0.01	

1.1.9 Economic model

This question was not prioritised for original economic analysis.

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

The number of newborn babies who develop late-onset neonatal infection was considered a key outcome as neonatal infection can have both short-term and long-term effects on health and quality of life. Length of hospital stay was also considered important as this can have an adverse impact on the baby and the baby's family as well as increased costs associated with a longer hospital stay.

Although antimicrobial resistance is an important factor to consider when examining the use of antibiotics, the committee decided that the information on rifampicin resistance was less important because rifampicin is not a commonly used antibiotic on neonatal units and any resistance should therefore have a minimal impact on the effects of antibiotic treatment in

newborn babies. Additionally, resistance in bacteria sampled from the catheter tips may not lead to infection with resistant bacteria, and so this outcome was considered less important.

1.1.10.2 The quality of the evidence

Two studies met the inclusion criteria, one Italian study examining the use of an umbilical vein catheter (UVC) impregnated with silver zeolite and one English-based study which used a peripherally inserted central catheter (PICC) impregnated with miconazole and rifampicin. The differences in clinical practice, type of catheter and type of antimicrobial used in each study meant that the results from each study could not be combined using meta-analysis, leaving limited evidence to assess the effectiveness of each of the interventions.

Evidence for the miconazole and rifampicin impregnated PICC (Gilbert 2019) was of high quality, had a large sample size and was fully applicable to the research question. This study did not restrict the inclusion criteria based on gestational age, but 88% of babies had a gestational age of less than 32 weeks. The findings from this study are therefore most applicable to very premature babies.

Evidence for the silver zeolite impregnated UVC (Bertini 2013) had a relatively small sample size. The quality of the evidence was downgraded due to limited information about the randomisation process and a partly subjective outcome of definite or probable infection (with probable infection based on clinical signs of infection) in a study where outcome assessors were not blinded to the intervention. The quality was also downgraded for partial applicability to the research question as neonatal units in Italy often use longer courses of antibiotics than those used in the UK. The infection rates reported were higher than those in the UK, which may be partly due to changes in infection control since the study was published in 2013. The prematurity of the babies was also raised by the committee as only infants with a gestational age of less than 30 weeks were included in the trial. Very premature babies have a higher infection rate than those closer to term and so it was more likely that the study would have an effect than might be apparent in babies born at a later gestational age. The findings of this study therefore were not only low quality but could also only be applied to a very premature population.

1.1.10.3 Imprecision and clinical importance of effects

No published minimally important differences were found and none prespecified by the committee. When examining the evidence from each study the committee discussed the effect sizes and confidence intervals for each outcome to determine whether the results were clinically meaningful. For the miconazole and rifampicin impregnated PICC, the effect sizes for most outcomes were close to the line of no effect and confidence intervals spanned both sides of the line. One outcome (antimicrobial resistance in cultures taken from the PICC tip) did show a difference between the 2 catheters, indicating less antimicrobial resistant cultures in the standard than the impregnated catheter. This could indicate a potentially negative effect of the impregnated catheter. However, the committee did not think that this alone was enough to be considered a negative outcome for the patient because resistant cultures taken from blood or cerebrospinal fluid (CSF) could not differentiate between babies given the standard or impregnated catheters.

For the silver zeolite impregnated UVC, the confidence intervals for both late-onset infection, mortality and length of stay outcomes were wider than those reported for the miconazole and rifampicin impregnated PICC. The committee discussed the greater imprecision of the results for the silver zeolite impregnated catheter and agreed that further research is needed before it is possible to be confident of the effects of this catheter. Despite the wide confidence

intervals, results still favoured the impregnated catheter over the standard catheter for late-onset neonatal infection and length of stay but not for the other outcomes. The committee decided that more, higher quality, evidence was needed before they could make a clinical recommendation and instead decided to make a research recommendation about the effects of silver zeolite-impregnated catheters (Appendix K).

1.1.10.4 Benefits and harms

There was no evidence of benefit for miconazole and rifampicin impregnated PICCs over non-impregnated PICCs. Evidence could not differentiate between an impregnated or standard PICC for the number of newborn babies developing late-onset infection or mortality. A potential harm was a greater number of cultures taken from the PICC tip with evidence of rifampicin resistance. However, this outcome was from one study and had wide confidence intervals, giving uncertainty over the result. In addition, rifampicin is not a commonly used antibiotic for systemic infections in newborn babies, and although there was a difference in resistance at the PICC tip, there was no clear difference between the levels of rifampicin resistance in the blood and CSF cultures of babies. The committee therefore did not consider this a serious harm.

Evidence for silver zeolite impregnated umbilical CVCs indicated that they could provide benefits by reducing the number of newborn babies developing late-onset infection, and by reducing length of stay in comparison to a non-impregnated umbilical CVC. Reducing the number of infections and the length of time spent in the neonatal unit could also result in reduced treatment costs for babies. The committee agreed that overall, the evidence favoured catheters impregnated with silver zeolite, with the results appearing to be clinically meaningful, which could serve to reduce the number of late-onset neonatal infections. However, given the small sample size in the single study on this catheter type, the relatively wide confidence intervals, and the inclusion of only very premature babies, the committee decided that further evidence would be needed before it could recommend their use. This led to the committee developing a research recommendation to establish their effectiveness (Appendix K).

1.1.10.5 Cost effectiveness and resource use

The committee was aware that impregnated catheters are more expensive than standard catheters. However, it agreed that any meaningful reduction in infections would be likely to justify increased expenditure (committee members noted that, in older children, the CATCH RCT had provided some support for this proposition). In the case of neonatal use, however, there was no evidence that impregnated PICCs are associated with lower rates of infection, so it is not possible to argue that their acquisition costs are offset. The committee agreed that a 5-fold reduction in infections, as seen with silver zeolite impregnated UVCs in Bertini et al. (2013), is likely to be associated with lower net costs, as evident in the shorter duration of hospital stay observed with impregnated catheters. However, as noted above, the committee agreed that it would be important to replicate this finding in a setting that is directly relevant to the present-day NHS before recommending these catheters for newborn babies. Therefore, the committee made a research recommendation (detailed in Appendix K) and specified that this research should include collection of data on resource-use and costs.

1.1.10.6 Other factors the committee took into account

Only 3 studies met the inclusion criteria for the use of antimicrobial-impregnated catheters in comparison with non-impregnated catheters for the prevention of late-onset infections in newborn babies. Results for the silver zeolite impregnated catheter indicated that it could

reduce the number of newborn babies with late-onset infection and the length of stay. Although the committee agreed that these outcomes are important, it was concerned over the limited evidence base because, despite the apparent benefits, no other studies have been published in relation to the use of silver zeolite in CVCs. Without further evidence that is more applicable to the healthcare system in the UK, the committee did not feel confident that it could recommend the use of these type of catheters. Instead, it included a research recommendation which may help to increase understanding of the use of silver zeolite impregnated catheters in newborn babies and potentially inform recommendations in future guideline updates (Appendix K).

The committee also commented on the lack of direct comparisons between different types of catheters. The 3 included studies compared an impregnated catheter and a matching, non-impregnated, catheter. Consequently, there is currently a lack of information regarding which type of catheter is the most effective in newborn babies and whether the effects of antimicrobial impregnation may vary depending on the type of catheter used. For this reason, the research recommendation did not state what type of catheter should be used to leave open the field for future research (Appendix K).

Another issue discussed by the committee is whether monotherapy is the most effective method of catheter impregnation or whether antibiotics may be more effective when used alongside other antimicrobials. Miconazole was used alongside rifampicin in the evidence for impregnated PICCs but few babies included in the trial had a fungal bloodstream infection and so there may have been other antimicrobials that would have been more effective when used in combination with rifampicin. The committee noted that, in the CATCH RCT in older children, a catheter impregnated with 2 antibiotics was shown to reduce infections. However, the impregnated PICC that was chosen for this study is the only one that is currently available in the UK for use with newborn babies. The research recommendation has therefore been designed so that either a single antimicrobial or a combination of antimicrobials can be used to impregnate the catheter. This should help increase understanding of the best methods of reducing neonatal catheter-related bloodstream infection.

The committee also highlighted that antimicrobial-impregnated catheters are recommended for use in adults and children and there is good evidence for their use in these populations. Much smaller catheters are required when treating newborn babies and so fewer are currently available. The silver zeolite catheter used in the study by Bertini was a central catheter for peripheral insertion which was used ‘off label’ as an UVC for the purposes of the trial. No central catheters impregnated with silver zeolite are licensed for use with newborn babies in the UK. With a limited choice of catheters there is also less variety in the types of antimicrobials that have been used to impregnate the catheter. With the higher rates of infection reported for newborn babies than for adults or children, and the serious consequences of neonatal infection, the committee agreed that the use of impregnated catheters as a potential method of reducing the incidence of neonatal infection needs examining in more detail.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendation 1.5.1 and the research recommendations on the effectiveness of antimicrobial-impregnated catheters and the effectiveness of catheters impregnated with silver zeolite (Appendix K).

1.1.12 References – included studies

1.1.12.1 Effectiveness

Bertini, Giovanna, Elia, Serena, Ceciarini, Federica et al. (2013) Reduction of catheter-related bloodstream infections in preterm infants by the use of catheters with the AgION antimicrobial system. Early human development 89(1): 21-5

Gilbert R., Brown M., Rainford N. et al. (2019) Antimicrobial-impregnated central venous catheters for prevention of neonatal bloodstream infection (PREVAIL): an open-label, parallel-group, pragmatic, randomised controlled trial. The Lancet Child and Adolescent Health 3(6): 381-390

Klemme, M., Staffler, A., De Maio, N. et al. (2020) Use of impregnated catheters to decrease colonization rates in neonates - A randomized controlled pilot trial. Journal of Neonatal-Perinatal Medicine 13(2): 231-237

Appendices

Appendix A – Review protocols

Review protocol for What is the clinical and cost effectiveness of intravascular catheters impregnated with antibiotics in reducing the risk of the baby developing late-onset neonatal infection?

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Prophylaxis for catheter-associated late-onset neonatal infection
2.	Review question	8.1 What is the clinical and cost effectiveness of intravascular catheters impregnated with antibiotics in reducing the risk of the baby developing late-onset neonatal infection?
3.	Objective	To evaluate the clinical and cost effectiveness of intravascular catheters impregnated with antibiotics in reducing the risk of late-onset neonatal infection Considerations to include: • effectiveness of impregnated intravascular catheter versus non-impregnated intravascular catheter

		• which class or classes of antimicrobial are used to impregnate the catheter
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE (including 'in process' and 'E-pub ahead of print') • Database of Abstracts of Reviews of Effect (DARE) Searches will be restricted by: • English language • Human studies Other searches: None

		The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review. No date restrictions have been applied for this question.
5.	Condition or domain being studied	Neonatal infection is a significant cause of mortality and morbidity in neonates. Late-onset neonatal infection occurs more than 72 hours after birth and can lead to life-threatening sepsis which accounts for 10% of all neonatal deaths.
6.	Population	Inclusion: • Term babies up to 28 days of age and preterm babies up to 28 days corrected gestational age who have had or are having an intravascular catheter inserted Exclusion: • Babies with suspected or confirmed non-bacterial infections. • Babies with localised infections.
7.	Intervention	Intravascular catheter impregnated with antibiotics, including:

		• Rifampicin (with or without miconazole) • Minocycline-rifampicin
8.	Comparator	Head-to-head comparison with any other impregnated intravascular catheter Non-impregnated intravascular catheters
9.	Types of study to be included	Randomised controlled trials (RCTs) Systematic reviews of RCTs will be used as an additional source of studies for cross checking against the search results. If systematic reviews are assessed as high quality (as assessed using the ROBIS checklist) and up to date they will be considered for use directly as a source of data (for full details, see the methods section of the evidence review). If no RCTs are found then observational studies will be included
10.	Other exclusion criteria	• Non-English language studies • Conference abstracts, theses, dissertations.
11.	Context	Neonatal units or neonatal intensive care units
12.	Primary outcomes (critical outcomes)	Neonatal outcomes:

		• culture-proven infection from sample taken between 72 hours (where available) and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection • antibiotics for suspected bloodstream infection . Measured between 72 hours (where available) and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection • mortality (while the catheter was in place and at the latest timepoint reported in study once the catheter was removed) • health-related quality of life, measured using a validated tool (while the catheter was in place and at the latest timepoint reported in study once the catheter was removed) • hospital length of stay

		• antimicrobial resistance (culture-proven or from the intravascular catheter) measured while the catheter was in place Family outcomes: • psychological distress in baby's family as measured using a validated scale (e.g. parental stressor scale NICU; modified Rutter Malaise Inventory) (while the catheter was in place and at the latest timepoint reported in study once the catheter was removed) •
13.	Secondary outcomes (important outcomes)	Not applicable. The committee did not wish to distinguish between critical and important outcomes as they considered all of the specified outcomes important for decision making.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing

		NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow. Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias. This review will make use of the priority screening functionality within the EPPI-reviewer software.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the Cochrane RoB v2.0 checklist as described in Developing NICE guidelines: the manual. The ROBIS checklist will be used to assess systematic reviews.
16.	Strategy for data synthesis	Meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-

		effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. Meta-analyses will be performed in Cochrane Review Manager V5.3
17.	Analysis of sub-groups	**Subgroups** • corrected age of the baby (<34 weeks, 34-37 weeks, >37 weeks) • Babies who have been admitted to hospital from home **Stratifications** • Data will be stratified according to type of antibiotic used.

		• Data will be stratified by antibiotic dose as follows: dose lower than that recommended in the summary of product characteristics (SPC), dose within the range recommended by the SPC, dose above the range recommended by the SPC
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	24/06/2019
22.	Anticipated completion date	12/08/2020

23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
		Piloting of the study selection process	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
		Formal screening of search results against eligibility criteria	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
		Data extraction	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
		Risk of bias (quality) assessment	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐

		Data analysis	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail** NIupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	From the Guideline Updates Team: • Dr Kathryn Hopkins • Dr Clare Dadswell • Mr Fadi Chehadah • Mr Gabriel Rogers • Mr Wesley Hubbard		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with		

		NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10111
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.

32.	Keywords	Intravascular catheters, antibiotics, early-onset neonatal infection
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

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Appendix B – Literature search strategies

Clinical search literature search strategy

The search was conducted on 2nd August 2019. The following databases were searched:

Medline, Medline In Process, Medline E-pub Ahead of print, Embase, (all via the Ovid platform), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, (both via the Wiley platform), and the DARE database (via the CRD platform).

Intervention and population terms

Medline, Medline in Process, Medline E-pub ahead of print

1 exp Infant, Newborn/

2 Term Birth/

3 Infant Care/

4 Perinatal Care/

5 Intensive Care Units, Neonatal/

6 Intensive Care, Neonatal/

7 Infant Health/

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw.

9 ((premature or pre-mature* or preterm or pre-term) adj4 (child* or infant* or baby* or babies* or offspring)).tw.

10 or/1-9

11 exp Bacterial Infections/

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw.

13 exp Sepsis/

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw.

15 (septic* adj4 shock*).tw.

16 or/11-15

17 exp Streptococcus/

18 exp Staphylococcus/

19 (streptococc* or staphylococc*).tw.

20 (GBS or MRSA or NRCS-A or MSSA).tw.

21 (met?icillin-resistant adj3 aureus).tw.

22 exp Escherichia coli/

23 ((Escheric* or E) adj2 coli).tw.

24 exp Listeria/

25 listeria*.tw.

26 exp Klebsiella/

27 klebsiella*.tw.

28 exp Pseudomonas/

29 (pseudomonas or chryseomonas or flavimonas).tw.

30 Enterobacteriaceae/

31 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw.

32 ((enteric or coliform) adj2 bac*).tw.

33 exp Neisseria/

34 neisseria*.tw.

35 exp Haemophilus influenzae/

36 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw.

37 exp Serratia/

38 serratia*.tw.

39 exp Cronobacter/

40 (cronobact* or sakazaki* or malonatic*).tw.

41 exp Acinetobacter/

42 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw.

43 exp Fusobacterium/

44 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw.

45 exp Enterococcus/

46 enterococc*.tw.

47 or/17-46

48 16 or 47

49 10 and 48

50 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw.

51 ((premature or pre-mature* or preterm or pre-term) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw.

52 50 or 51

53 49 or 52

54 (bacter?emia* or bacill?emia*).tw.

55 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw.

56 54 or 55

57 56 and 10

58 53 or 57

59 exp Catheters/

60 Catheterization/

61 Catheterization, Central Venous/

62 exp Catheterization, Peripheral/

63 (catheter* or cannula*).tw.

64 ((peripheral* or percutaneous) adj4 (insert* or plac* or indwell* or in-dwell* or punctur* or arterial or venous)).tw.

65 (central* adj1 (vein* or venous or arterial) adj4 (insert* or plac* or indwell* or in-dwell* or punctur*)).tw.

66 (PICC* or EPIV* or PIV or PIVs or CVC or CVCs).tw.

67 (PIC* adj2 lin*).tw.

68 Catheter-Related Infections/

69 (CRBSI* or CR-BSI* or CLABSI* or CLA-BSI* or CABSI* or CRI or CRIs or CRB*).tw.

70 or/59-69

71 58 and 70

72 Animals/ not Humans/

73 71 not 72

74 limit 73 to english language

Embase

1 newborn/

2 term birth/

3 infant care/

4 perinatal care/

5 neonatal intensive care unit/

6 newborn intensive care/

7 child health/

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw.

9 ((premature or pre-mature* or preterm or pre-term) adj4 (child* or infant* or baby* or babies* or offspring)).tw.

10 or/1-9

11 exp bacterial infection/

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw.

13 exp sepsis/

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw.

15 (septic* adj4 shock*).tw.

16 or/11-15

17 exp Streptococcus/

18 exp Staphylococcus/

19 (streptococc* or staphylococc*).tw.

20 (GBS or MRSA or NRCS-A or MSSA).tw.

21 (met?icillin-resistant adj3 aureus).tw.

22 exp Escherichia coli/

23 ((Escheric* or E) adj2 coli).tw.

24 exp Listeria/

25 listeria*.tw.

26 exp Klebsiella/

27 klebsiella*.tw.

28 exp Pseudomonas/

29 (pseudomonas or chryseomonas or flavimonas).tw.

30 exp Enterobacteriaceae/

31 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw.

32 ((enteric or coliform) adj2 bac*).tw.

33 exp Neisseria/

34 neisseria*.tw.

35 exp Haemophilus influenzae/

36 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw.

37 exp Serratia/

38 serratia*.tw.

39 exp cronobacter/

40 (cronobact* or sakazaki* or malonatic*).tw.

41 exp Acinetobacter/

42 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw.

43 exp Fusobacterium/

44 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw.

45 exp Enterococcus/

46 enterococc*.tw.

47 or/17-46

48 16 or 47

49 10 and 48

50 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw.

51 ((premature or pre-mature* or preterm or pre-term) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw.

52 50 or 51

53 49 or 52

54 (bacter?emia* or bacill?emia*).tw.

55 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw.

56 54 or 55

57 56 and 10

58 53 or 57

59 exp catheter/

60 catheterization/

61 central venous catheterization/

62 (catheter* or cannula*).tw.

63 ((peripheral* or percutaneous) adj4 (insert* or plac* or indwell* or in-dwell* or punctur* or arterial or venous)).tw.

64 (central* adj1 (vein* or venous or arterial) adj4 (insert* or plac* or indwell* or in-dwell* or punctur*)).tw.

65 (PICC* or EPIV* or PIV or PIVs or CVC or CVCs).tw.

66 (PIC* adj2 lin*).tw.

67 catheter infection/

68 (CRBSI* or CR-BSI* or CLABSI* or CLA-BSI* or CABSI* or CRI or CRIs or CRB*).tw.

69 or/59-68

70 58 and 69

71 nonhuman/ not human/

72 70 not 71

73 limit 72 to english language

Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials

#1 MeSH descriptor: [Infant, Newborn] explode all trees

#2 MeSH descriptor: [Term Birth] this term only

#3 MeSH descriptor: [Infant Care] this term only

#4 MeSH descriptor: [Perinatal Care] this term only

#5 MeSH descriptor: [Intensive Care Units, Neonatal] this term only

#6 MeSH descriptor: [Intensive Care, Neonatal] this term only

#7 MeSH descriptor: [Infant Health] this term only

#8 ((newborn* or new born* or new-born or neonat* or neo-nat* or perinat* or peri-nat*)):ti,ab,kw

#9 ((premature or pre-mature* or preterm or pre-term) near/4 (child* or infant* or baby* or babies* or offspring)):ti,ab,kw

#10 {or #1-#9}

#11 MeSH descriptor: [Bacterial Infections] explode all trees

#12 ((bacter* or strep* or staph* or GNB) near/4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)):ti,ab,kw

#13 MeSH descriptor: [Sepsis] explode all trees

#14 ((sepsis or septic?emia* or py?emia* or pyho?emia*)):ti,ab,kw

#15 ((septic* near/4 shock*)):ti,ab,kw

#16 {or #11-#15}

#17 MeSH descriptor: [Streptococcus] explode all trees

#18 MeSH descriptor: [Staphylococcus] explode all trees

#19 ((streptococc* or staphylococc*)):ti,ab,kw

#20 ((GBS or MRSA or NRCS-A or MSSA)):ti,ab,kw

#21 ((met?icillin-resistant near/3 aureus)):ti,ab,kw

#22 MeSH descriptor: [Escherichia coli] explode all trees

#23 ((Escheric* or E) near/2 (coli)):ti,ab,kw

#24 MeSH descriptor: [Listeria] explode all trees

#25 (Listeria*):ti,ab,kw

#26 MeSH descriptor: [Klebsiella] explode all trees

#27 (klebsiella*):ti,ab,kw

#28 MeSH descriptor: [Pseudomonas] explode all trees

#29 ((pseudomonas or chryseomonas or flavimonas)):ti,ab,kw

#30 MeSH descriptor: [Enterobacteriaceae] explode all trees

#31 ((enterobact* or sodalis or paracolobactrum or ewingella or leclercia)):ti,ab,kw

#32 ((enteric or coliform) near/2 (bac*)):ti,ab,kw

#33 MeSH descriptor: [Neisseria] explode all trees

#34 (neisseria*):ti,ab,kw

#35 MeSH descriptor: [Haemophilus influenzae] explode all trees

#36 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) near/2 (influenz* or pfeiffer* or meningitidis)):ti,ab,kw

#37 MeSH descriptor: [Serratia] explode all trees

#38 (serratia*):ti,ab,kw

#39 MeSH descriptor: [Cronobacter] explode all trees

#40 ((cronobact* or sakazaki* or malonatic*)):ti,ab,kw

#41 MeSH descriptor: [Acinetobacter] explode all trees

#42 ((acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*)):ti,ab,kw

#43 MeSH descriptor: [Fusobacterium] explode all trees

#44 ((fusobact* or sphaerophor* or necrophorum or nucleatum)):ti,ab,kw

#45 MeSH descriptor: [Enterococcus] explode all trees

#46 (enterococc*):ti,ab,kw

#47 {or #17-#46}

#48 #16 or #47

#49 #10 and #48

#50 ((newborn* or new born* or new-born* or neonat* or neo-nat* or perinat* or peri-nat*) near/4 (infect*)):ti,ab,kw

#51 ((premature or pre-mature* or preterm or pre-term) near/4 (child* or infant* or baby* or babies* or offspring) near/4 (infect*)):ti,ab,kw

#52 #50 or #51

#53 #49 or #52

#54 ((bacter?emia* or bacill?emia*)):ti,ab,kw

#55 ((blood*) near/4 (infect* or contamin* or invas* or invad*)):ti,ab,kw

#56 #54 or #55

#57 #10 and #56

#58 #53 or #57

#59 MeSH descriptor: [Catheters] explode all trees

#60 MeSH descriptor: [Catheterization] this term only

#61 MeSH descriptor: [Catheterization, Central Venous] this term only

#62 MeSH descriptor: [Catheterization, Peripheral] explode all trees

#63 ((catheter* or cannula*)):ti,ab,kw

#64 ((peripheral* or percutaneous) near/4 (insert* or plac* or indwell* or in-dwell* or punctur* or arterial or venous)):ti,ab,kw

#65 ((central*) near/1 (vein* or venous or arterial) near/4 (insert* or plac* or indwell* or in-dwell* or punctur*)):ti,ab,kw

#66 ((PICC* or EPIV* or PIV or PIVs or CVC or CVCs)):ti,ab,kw1307

#67 ((PIC* near/2 lin*)):ti,ab,kw

#68 MeSH descriptor: [Catheter-Related Infections] this term only

#69 ((CRBSI* or CR-BSI* or CLABSI* or CLA-BSI* or CABSI* or CRI or CRIs or CRB*)):ti,ab,kw

#70 {or #59-#69}

#71 #58 and #70

#72 (conference):pt

#73 ((clinicaltrials or trialsearch)):so

#74 #72 or #73

#75 #71 not #74

DARE

1 MeSH DESCRIPTOR Infant, Newborn EXPLODE ALL TREES

2 MeSH DESCRIPTOR Term Birth

3 MeSH DESCRIPTOR Infant Care

4 MeSH DESCRIPTOR Perinatal Care

5 MeSH DESCRIPTOR Intensive Care Units, Neonatal

6 MeSH DESCRIPTOR Intensive Care, Neonatal

7 MeSH DESCRIPTOR Infant Health

8 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*))

9 ((premature or pre-mature* or preterm or pre-term) NEAR4 (child* or infant* or baby* or babies* or offspring))

10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

11 MeSH DESCRIPTOR Bacterial Infections EXPLODE ALL TREES

12 ((bacter* or strep* or staph* or GNB) NEAR4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*))

13 MeSH DESCRIPTOR Sepsis EXPLODE ALL TREES

14 ((sepsis or septic?emia* or py?emia* or pyho?emia*))

15 ((septic* NEAR4 shock*))

16 #11 OR #12 OR #13 OR #14 OR #15

17 MeSH DESCRIPTOR Streptococcus EXPLODE ALL TREES

18 MeSH DESCRIPTOR Staphylococcus EXPLODE ALL TREES

19 ((streptococc* or staphylococc*))

20 ((GBS or MRSA or NRCS-A or MSSA))

21 ((met?icillin-resistant NEAR3 aureus))

22 MeSH DESCRIPTOR Escherichia coli EXPLODE ALL TREES

23 ((Escheric* or E) NEAR2 (coli))

24 MeSH DESCRIPTOR Listeria EXPLODE ALL TREES

25 (listeria*)

26 MeSH DESCRIPTOR Klebsiella EXPLODE ALL TREES

27 (klebsiella*)

28 MeSH DESCRIPTOR Pseudomonas EXPLODE ALL TREES

29 ((pseudomonas or chryseomonas or flavimonas))

30 MeSH DESCRIPTOR Enterobacteriaceae EXPLODE ALL TREES

31 ((enterobact* or sodalis or paracolobactrum or ewingella or leclercia))

32 ((enteric or coliform) NEAR2 (bac*))

33 MeSH DESCRIPTOR Neisseria EXPLODE ALL TREES

34 (neisseria*)

35 MeSH DESCRIPTOR Haemophilus influenzae EXPLODE ALL TREES

36 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) NEAR2 (influenz* or pfeiffer* or meningitidis))

37 MeSH DESCRIPTOR Serratia EXPLODE ALL TREES

38 (serratia*)

39 MeSH DESCRIPTOR Cronobacter EXPLODE ALL TREES

40 ((cronobact* or sakazaki* or malonatic*))

41 MeSH DESCRIPTOR Acinetobacter EXPLODE ALL TREES

42 ((acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*))

43 MeSH DESCRIPTOR Fusobacterium EXPLODE ALL TREES

44 ((fusobact* or sphaerophor* or necrophorum or nucleatum))

45 MeSH DESCRIPTOR Enterococcus EXPLODE ALL TREES

46 (enterococc*)

47 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46

48 #16 OR #47

49 #10 AND #48

50 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) NEAR4 (infect*))

51 ((premature or pre-mature* or preterm or pre-term) NEAR4 (child* or infant* or baby* or babies* or offspring) NEAR4 (infect*))

52 #50 OR #51

53 #49 OR #52

54 ((bacter?emia* or bacill?emia*))

55 ((blood*) NEAR4 (infect* or contamin* or invas* or invad*))

56 #54 OR #55

57 #10 AND #56

58 #53 OR #57

59 MeSH DESCRIPTOR Catheters EXPLODE ALL TREES

60 MeSH DESCRIPTOR Catheterization

61 MeSH DESCRIPTOR Catheterization, Central Venous

62 MeSH DESCRIPTOR Catheterization, Peripheral EXPLODE ALL TREES

63 ((catheter* or cannula*))

64 ((peripheral* or percutaneous) NEAR4 (insert* or plac* or indwell* or in-dwell* or punctur* or arterial or venous))

65 ((central*) NEAR1 (vein* or venous or arterial) NEAR4 (insert* or plac* or indwell* or in-dwell* or punctur*))

66 ((PICC* or EPIV* or PIV or PIVs or CVC or CVCs))

67 ((PIC*) NEAR2 (lin*))

68 MeSH DESCRIPTOR Catheter-Related Infections

69 ((CRBSI* or CR-BSI* or CLABSI* or CLA-BSI* or CABSI* or CRI or CRIs or CRB*))

70 #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69

71 #58 AND #70

72 * IN DARE

73 #71 AND #72

Search Filters

The following search filters were combined as 'And' with the population and intervention terms for the Medline databases and Embase. Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and DARE are systematic review or randomised controlled trial databases so did not require the addition of a filter.

The Medline versions of the filters are reproduced below. Embase has validated translations of these that were used in the search.

Randomised Controlled Trial

1. randomized controlled trial.pt.

2. randomi?ed.mp.

3. placebo.mp.

4. or/1-3

Systematic Review

1 MEDLINE or pubmed).tw.

2 systematic review.tw.

3 systematic review.pt.

4 meta-analysis.pt.

5 intervention$.ti.

6 or/1-5

Health Economics literature search strategy

Sources searched to identify economic evaluations

- MEDLINE (Ovid)
- MEDLINE in Process (Ovid)
- Medline E-pubs (Ovid)
- Embase (Ovid)
- EconLit (Ovid)

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update in July 2019. Search filters to retrieve economic evaluations and quality of life papers were appended to the population and intervention terms to identify relevant evidence. Searches were not undertaken for qualitative RQs. Searches were re-run in July 2020 where the filters were added to the population terms.

Health economics search strategy

Database: Medline (Ovid)
1 exp Infant, Newborn/ (607120)
2 Term Birth/ (2958)
3 Infant Care/ (9209)
4 Perinatal Care/ (4613)
5 Intensive Care Units, Neonatal/ (14748)
6 Intensive Care, Neonatal/ (5673)
7 Infant Health/ (783)
8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (394580)
9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (50922)
10 or/1-9 (791905)
11 exp Bacterial Infections/ (886598)
12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (148920)
13 exp Sepsis/ (123123)
14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (100090)
15 (septic* adj4 shock*).tw. (19697)
16 (bacter?emia* or bacill?emia*).tw. (26877)
17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (38725)
18 or/11-17 (1097119)
19 exp Streptococcus/ (78627)
20 exp Staphylococcus/ (104852)
21 (streptococc* or staphylococc*).tw. (206696)

22 (GBS or MRSA or NRCS-A or MSSA).tw. (27020)

23 (met?icillin-resistant adj3 aureus).tw. (23563)

24 exp Escherichia coli/ (278943)

25 (((Escheric* or E) adj2 coli) or ecoli*).tw. (289781)

26 exp Listeria/ (15143)

27 listeria*.tw. (18688)

28 exp Klebsiella/ (19836)

29 klebsiella*.tw. (26962)

30 exp Pseudomonas/ (71592)

31 (pseudomonas or chryseomonas or flavimonas).tw. (85911)

32 Enterobacteriaceae/ (18945)

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (30291)

34 ((enteric or coliform) adj2 bac*).tw. (5982)

35 exp Neisseria/ (20482)

36 neisseria*.tw. (18785)

37 exp Haemophilus influenzae/ (13731)

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (19500)

39 exp Serratia/ (6599)

40 serratia*.tw. (8439)

41 exp Cronobacter/ (655)

42 (cronobact* or sakazaki* or malonatic*).tw. (958)

43 exp Acinetobacter/ (9822)

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (15154)

45 exp Fusobacterium/ (3796)

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (5425)

47 exp Enterococcus/ (19718)

48 enterococc*.tw. (26150)

49 or/19-48 (765874)

50 18 or 49 (1614537)

51 10 and 50 (65444)

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (16079)

53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (946)

54 52 or 53 (16770)

55 51 or 54 (74853)

56 Economics/ (27206)

57 exp "Costs and Cost Analysis"/ (237006)

58 Economics, Dental/ (1911)

59 exp Economics, Hospital/ (24558)

60 exp Economics, Medical/ (14206)

61 Economics, Nursing/ (3999)

62 Economics, Pharmaceutical/ (2941)

63 Budgets/ (11315)

64 exp Models, Economic/ (15053)

65 Markov Chains/ (14321)

66 Monte Carlo Method/ (28322)

67 Decision Trees/ (11133)

68 econom$.tw. (238765)

69 cba.tw. (9764)

70 cea.tw. (20532)

71 cua.tw. (999)

72 markov$.tw. (17997)

73 (monte adj carlo).tw. (29925)

74 (decision adj3 (tree$ or analys$)).tw. (13431)

75 (cost or costs or costing$ or costly or costed).tw. (460618)

76 (price$ or pricing$).tw. (33468)

77 budget$.tw. (23716)

78 expenditure$.tw. (49355)

79 (value adj3 (money or monetary)).tw. (2096)

80 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3485)

81 or/56-80 (926379)

82 "Quality of Life"/ (194718)

83 quality of life.tw. (229884)

84 "Value of Life"/ (5706)

85 Quality-Adjusted Life Years/ (12284)

86 quality adjusted life.tw. (10842)

87 (qaly$ or qald$ or qale$ or qtime$).tw. (8901)

88 disability adjusted life.tw. (2741)

89 daly$.tw. (2486)

90 Health Status Indicators/ (23409)

91 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (22454)

92 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1323)

93 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4902)

94 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (29)

95 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (381)

96 (euroqol or euro qol or eq5d or eq 5d).tw. (9001)

97 (qol or hql or hqol or hrqol).tw. (44126)

98 (hye or hyes).tw. (60)

99 health$ year$ equivalent$.tw. (38)

100 utilit$.tw. (171457)

101 (hui or hui1 or hui2 or hui3).tw. (1304)

102 disutili$.tw. (396)

103 rosser.tw. (94)

104 quality of wellbeing.tw. (14)

105 quality of well-being.tw. (381)

106 qwb.tw. (190)

107 willingness to pay.tw. (4500)

108 standard gamble$.tw. (783)

109 time trade off.tw. (1037)

110 time tradeoff.tw. (238)

111 tto.tw. (899)

112 or/82-111 (493012)

113 81 or 112 (1350947)

114 55 and 113 (3480)

115 limit 114 to ed=20190716-20200724 (226)

116 animals/ not humans/ (4686781)

117 115 not 116 (213)

118 limit 117 to english language (208)

Database: MiP (Ovid)

1 exp Infant, Newborn/ (0)

2 Term Birth/ (0)

3 Infant Care/ (0)

4 Perinatal Care/ (0)

5 Intensive Care Units, Neonatal/ (0)

6 Intensive Care, Neonatal/ (0)

7 Infant Health/ (0)

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (32462)

9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (4347)

10 or/1-9 (34405)

11 exp Bacterial Infections/ (0)

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (17517)

13 exp Sepsis/ (0)

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (12331)

15 (septic* adj4 shock*).tw. (2749)

16 (bacter?emia* or bacill?emia*).tw. (2792)

17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (4519)

18 or/11-17 (35377)

19 exp Streptococcus/ (0)

20 exp Staphylococcus/ (0)

21 (streptococc* or staphylococc*).tw. (22112)

22 (GBS or MRSA or NRCS-A or MSSA).tw. (4384)

23 (met?icillin-resistant adj3 aureus).tw. (3264)

24 exp Escherichia coli/ (0)

25 (((Escheric* or E) adj2 coli) or ecoli*).tw. (21337)

26 exp Listeria/ (0)

27 listeria*.tw. (2351)

28 exp Klebsiella/ (0)

29 klebsiella*.tw. (4101)

30 exp Pseudomonas/ (0)

31 (pseudomonas or chryseomonas or flavimonas).tw. (10779)

32 Enterobacteriaceae/ (0)

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (4282)

34 ((enteric or coliform) adj2 bac*).tw. (585)

35 exp Neisseria/ (0)

36 neisseria*.tw. (1256)

37 exp Haemophilus influenzae/ (0)

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (1064)

39 exp Serratia/ (0)

40 serratia*.tw. (829)

41 exp Cronobacter/ (0)

42 (cronobact* or sakazaki* or malonatic*).tw. (168)

43 exp Acinetobacter/ (0)

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (2747)

45 exp Fusobacterium/ (0)

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (821)

47 exp Enterococcus/ (0)

48 enterococc*.tw. (3589)

49 or/19-48 (59520)

50 18 or 49 (83682)

51 10 and 50 (2543)

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (1246)

53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (81)

54 52 or 53 (1309)

55 51 or 54 (3367)

56 Economics/ (0)

57 exp "Costs and Cost Analysis"/ (0)

58 Economics, Dental/ (0)

59 exp Economics, Hospital/ (0)

60 exp Economics, Medical/ (0)

61 Economics, Nursing/ (0)

62 Economics, Pharmaceutical/ (0)

63 Budgets/ (0)

64 exp Models, Economic/ (0)

65 Markov Chains/ (1)

66 Monte Carlo Method/ (2)

67 Decision Trees/ (0)

68 econom$.tw. (47080)

69 cba.tw. (456)

70 cea.tw. (2004)

71 cua.tw. (198)

72 markov$.tw. (5795)

73 (monte adj carlo).tw. (17215)

74 (decision adj3 (tree$ or analys$)).tw. (2609)

75 (cost or costs or costing$ or costly or costed).tw. (99726)

76 (price$ or pricing$).tw. (6047)

77 budget$.tw. (5074)

78 expenditure$.tw. (6509)

79 (value adj3 (money or monetary)).tw. (364)

80 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (502)

81 or/56-80 (172313)

82 "Quality of Life"/ (0)

83 quality of life.tw. (40043)

84 "Value of Life"/ (0)

85 Quality-Adjusted Life Years/ (0)

86 quality adjusted life.tw. (1728)

87 (qaly$ or qald$ or qale$ or qtime$).tw. (1455)

88 disability adjusted life.tw. (523)

89 daly$.tw. (479)

90 Health Status Indicators/ (0)

91 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (2735)

92 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (779)

93 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (773)

94 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (5)

95 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (20)

96 (euroqol or euro qol or eq5d or eq 5d).tw. (1711)

97 (qol or hql or hqol or hrqol).tw. (7636)

98 (hye or hyes).tw. (8)

99 health$ year$ equivalent$.tw. (2)

100 utilit$.tw. (32031)

101 (hui or hui1 or hui2 or hui3).tw. (203)

102 disutili$.tw. (60)

103 rosser.tw. (4)

104 quality of wellbeing.tw. (9)

105 quality of well-being.tw. (29)

106 qwb.tw. (13)

107 willingness to pay.tw. (957)

108 standard gamble$.tw. (62)

109 time trade off.tw. (119)

110 time tradeoff.tw. (11)

111 tto.tw. (145)

112 or/82-111 (74419)

113 81 or 112 (236895)

114 55 and 113 (231)

115 limit 114 to dt=20190716-20200724 (89)

116 animals/ not humans/ (1)

117 115 not 116 (89)

118 limit 117 to english language (89)

Database: Medline E-pubs (Ovid)
1 exp Infant, Newborn/ (0)
2 Term Birth/ (0)
3 Infant Care/ (0)
4 Perinatal Care/ (0)
5 Intensive Care Units, Neonatal/ (0)
6 Intensive Care, Neonatal/ (0)
7 Infant Health/ (0)
8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (6371)
9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (1421)
10 or/1-9 (6871)
11 exp Bacterial Infections/ (0)
12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (2219)
13 exp Sepsis/ (0)
14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (1706)
15 (septic* adj4 shock*).tw. (361)
16 (bacter?emia* or bacill?emia*).tw. (347)
17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (688)
18 or/11-17 (4700)
19 exp Streptococcus/ (0)
20 exp Staphylococcus/ (0)
21 (streptococc* or staphylococc*).tw. (2264)
22 (GBS or MRSA or NRCS-A or MSSA).tw. (468)
23 (met?icillin-resistant adj3 aureus).tw. (345)
24 exp Escherichia coli/ (0)

25 (((Escheric* or E) adj2 coli) or ecoli*).tw. (2275)

26 exp Listeria/ (0)

27 listeria*.tw. (198)

28 exp Klebsiella/ (0)

29 klebsiella*.tw. (476)

30 exp Pseudomonas/ (0)

31 (pseudomonas or chryseomonas or flavimonas).tw. (1004)

32 Enterobacteriaceae/ (0)

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (460)

34 ((enteric or coliform) adj2 bac*).tw. (64)

35 exp Neisseria/ (0)

36 neisseria*.tw. (177)

37 exp Haemophilus influenzae/ (0)

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (149)

39 exp Serratia/ (0)

40 serratia*.tw. (72)

41 exp Cronobacter/ (0)

42 (cronobact* or sakazaki* or malonatic*).tw. (14)

43 exp Acinetobacter/ (0)

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (290)

45 exp Fusobacterium/ (0)

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (112)

47 exp Enterococcus/ (0)

48 enterococc*.tw. (403)

49 or/19-48 (6238)

50 18 or 49 (9619)

51 10 and 50 (455)

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (255)

53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (16)

54 52 or 53 (268)

55 51 or 54 (651)

56 Economics/ (0)

57 exp "Costs and Cost Analysis"/ (0)

58 Economics, Dental/ (0)

59 exp Economics, Hospital/ (0)

60 exp Economics, Medical/ (0)

61 Economics, Nursing/ (0)

62 Economics, Pharmaceutical/ (0)

63 Budgets/ (0)

64 exp Models, Economic/ (0)

65 Markov Chains/ (0)

66 Monte Carlo Method/ (0)

67 Decision Trees/ (0)

68 econom$.tw. (6645)

69 cba.tw. (61)

70 cea.tw. (331)

71 cua.tw. (17)

72 markov$.tw. (718)

73 (monte adj carlo).tw. (1219)

74 (decision adj3 (tree$ or analys$)).tw. (519)

75 (cost or costs or costing$ or costly or costed).tw. (13246)

76 (price$ or pricing$).tw. (954)

77 budget$.tw. (555)

78 expenditure$.tw. (1143)

79 (value adj3 (money or monetary)).tw. (65)

80 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (51)

81 or/56-80 (21922)

82 "Quality of Life"/ (0)

83 quality of life.tw. (7520)

84 "Value of Life"/ (0)

85 Quality-Adjusted Life Years/ (0)

86 quality adjusted life.tw. (388)

87 (qaly$ or qald$ or qale$ or qtime$).tw. (329)

88 disability adjusted life.tw. (101)

89 daly$.tw. (88)

90 Health Status Indicators/ (0)

91 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (479)

92 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (50)

93 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (180)

94 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (1)

95 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (4)

96 (euroqol or euro qol or eq5d or eq 5d).tw. (407)

97 (qol or hql or hqol or hrqol).tw. (1460)

98 (hye or hyes).tw. (1)

99 health$ year$ equivalent$.tw. (0)

100 utilit$.tw. (4989)

101 (hui or hui1 or hui2 or hui3).tw. (18)

102 disutili$.tw. (12)

103 rosser.tw. (0)

104 quality of wellbeing.tw. (0)

105 quality of well-being.tw. (9)

106 qwb.tw. (3)

107 willingness to pay.tw. (184)

108 standard gamble$.tw. (7)

109 time trade off.tw. (20)

110 time tradeoff.tw. (2)

111 tto.tw. (18)

112 or/82-111 (12826)

113 81 or 112 (32909)

114 55 and 113 (55)

115 limit 114 to english language (55)

Database: Embase (Ovid)

1 newborn/ (526097)

2 term birth/ (3569)

3 infant care/ (1049)

4 perinatal care/ (14198)

5 neonatal intensive care unit/ (10192)

6 newborn intensive care/ (26405)

7 child health/ (27137)

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (536460)

9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (68782)

10 or/1-9 (841089)

11 exp bacterial infection/ (838120)

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (208658)

13 exp sepsis/ (263922)

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (168012)

15 (septic* adj4 shock*).tw. (36223)

16 (bacter?emia* or bacill?emia*).tw. (40194)

17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (61015)

18 or/11-17 (1201558)

19 exp Streptococcus/ (128274)

20 exp Staphylococcus/ (209430)

21 (streptococc* or staphylococc*).tw. (262126)

22 (GBS or MRSA or NRCS-A or MSSA).tw. (46092)

23 (met?icillin-resistant adj3 aureus).tw. (34157)

24 exp Escherichia coli/ (361361)

25 (((Escheric* or E) adj2 coli) or ecoli*).tw. (339772)

26 exp Listeria/ (24096)

27 listeria*.tw. (22102)

28 exp Klebsiella/ (59561)

29 klebsiella*.tw. (42289)

30 exp Pseudomonas/ (144052)

31 (pseudomonas or chryseomonas or flavimonas).tw. (118130)

32 Enterobacteriaceae/ (23812)

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (42447)

34 ((enteric or coliform) adj2 bac*).tw. (7285)

35 exp Neisseria/ (32218)

36 neisseria*.tw. (22936)

37 exp Haemophilus influenzae/ (29007)

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (24329)

39 exp Serratia/ (14280)

40 serratia*.tw. (10397)

41 exp cronobacter/ (817)

42 (cronobact* or sakazaki* or malonatic*).tw. (1214)

43 exp Acinetobacter/ (27955)

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (23888)

45 exp Fusobacterium/ (7678)

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (7403)

47 exp Enterococcus/ (49841)

48 enterococc*.tw. (37571)

49 or/19-48 (967441)

50 18 or 49 (1894492)

51 10 and 50 (70672)

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (21945)

53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (1283)

54 52 or 53 (22885)

55 51 or 54 (83775)

56 exp Health Economics/ (845404)

57 exp "Health Care Cost"/ (290992)

58 exp Pharmacoeconomics/ (202216)

59 Monte Carlo Method/ (40279)

60 Decision Tree/ (13001)

61 econom$.tw. (368838)

62 cba.tw. (12788)

63 cea.tw. (34786)

64 cua.tw. (1498)

65 markov$.tw. (30389)

66 (monte adj carlo).tw. (48341)

67 (decision adj3 (tree$ or analys$)).tw. (23602)

68 (cost or costs or costing$ or costly or costed).tw. (772396)

69 (price$ or pricing$).tw. (57398)

70 budget$.tw. (38616)

71 expenditure$.tw. (74588)

72 (value adj3 (money or monetary)).tw. (3455)

73 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (8625)

74 or/56-73 (1760062)

75 "Quality of Life"/ (469927)

76 Quality Adjusted Life Year/ (26663)

77 Quality of Life Index/ (2774)

78 Short Form 36/ (29036)

79 Health Status/ (127411)

80 quality of life.tw. (439622)

81 quality adjusted life.tw. (19747)

82 (qaly$ or qald$ or qale$ or qtime$).tw. (20178)

83 disability adjusted life.tw. (4103)

84 daly$.tw. (4016)

85 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (41434)

86 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2420)

87 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (9462)

88 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (61)

89 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (455)

90 (euroqol or euro qol or eq5d or eq 5d).tw. (20619)

91 (qol or hql or hqol or hrqol).tw. (97056)
92 (hye or hyes).tw. (135)
93 health$ year$ equivalent$.tw. (41)
94 utilit$.tw. (289831)
95 (hui or hui1 or hui2 or hui3).tw. (2300)
96 disutili$.tw. (924)
97 rosser.tw. (124)
98 quality of wellbeing.tw. (42)
99 quality of well-being.tw. (486)
100 qwb.tw. (253)
101 willingness to pay.tw. (8837)
102 standard gamble$.tw. (1104)
103 time trade off.tw. (1708)
104 time tradeoff.tw. (291)
105 tto.tw. (1683)
106 or/75-105 (989974)
107 74 or 106 (2593254)
108 55 and 107 (5731)
109 limit 108 to dc=20190716-20200724 (558)
110 nonhuman/ not human/ (4649157)
111 109 not 110 (522)
112 limit 111 to english language (510)
113 limit 112 to (conference abstract or conference paper or "conference review") (113)
114 112 not 113 (397)

Database: Econlit (Ovid)
1 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (732)
2 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (45)

3 1 or 2 (767)

4 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (49)

5 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (17)

6 (septic* adj4 shock*).tw. (1)

7 (bacter?emia* or bacill?emia*).tw. (3)

8 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (17)

9 (streptococc* or staphylococc*).tw. (18)

10 (GBS or MRSA or NRCS-A or MSSA).tw. (40)

11 (met?icillin-resistant adj3 aureus).tw. (8)

12 (((Escheric* or E) adj2 coli) or ecoli*).tw. (47)

13 listeria*.tw. (6)

14 klebsiella*.tw. (0)

15 (pseudomonas or chryseomonas or flavimonas).tw. (6)

16 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (1)

17 ((enteric or coliform) adj2 bac*).tw. (0)

18 neisseria*.tw. (1)

19 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (14)

20 serratia*.tw. (0)

21 (cronobact* or sakazaki* or malonatic*).tw. (1)

22 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (2)

23 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (0)

24 enterococc*.tw. (5)

25 or/4-24 (194)

26 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (11)

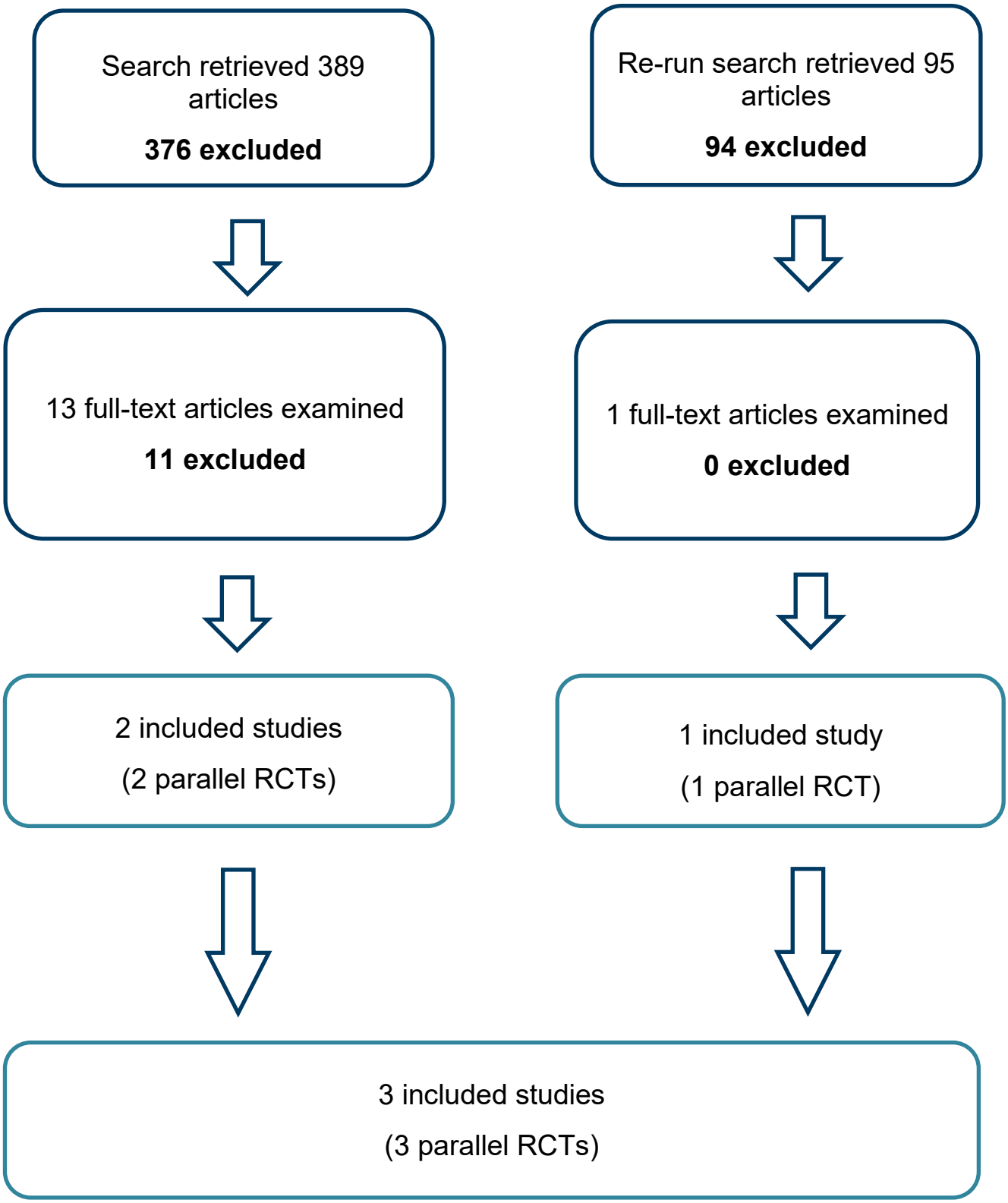
27 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (1)

28 26 or 27 (12)

29 25 or 28 (205)

30	3 and 29 (15)
31	limit 30 to yr="2019 -Current" (1)

Appendix C – Effectiveness evidence study selection



1 Appendix D – Effectiveness evidence

Bertini, 2013

2

Bibliographic Reference	Bertini, Giovanna; Elia, Serena; Ceciarini, Federica; Dani, Carlo; Reduction of catheter-related bloodstream infections in preterm infants by the use of catheters with the AgION antimicrobial system.; Early human development; 2013; vol. 89 (no. 1); 21-5

3 **Study details**

Study type	Randomised controlled trial (RCT)
Study location	Florence, Italy
Study setting	Neonatal Intensive Care Unit of the Careggi University Hospital
Study dates	July 2007 - June 2009
Duration of follow-up	Mean follow-up time 6.4 (±4.3) days
Sources of funding	None reported
Inclusion criteria	Infants with a gestational age ≤30 weeks who required an umbilical venous catheter in the first week of life for parenteral nutrition and/or therapy
Exclusion criteria	Major congenital malformations Hydrops fetalis Inherited congenital metabolic diseases Death during the first week of life
Sample size	98
Outcome measures	Neonatal length of stay Neonatal mortality Death before hospital discharge Culture-proven late-onset neonatal infection Finding of one culture of a peripheral, percutaneously-obtained blood sample that was positive for the same organism found to colonize the UVC tip with central line in place or within 48 hours of removal Suspected late-onset neonatal infection Occurrence of one positive UVC tip culture and negative or not concordant positive blood culture drawn from the UVC, clinical manifestations of infection, with a central line (connected to UVC) in place or within 48 h of central line removal

Study arms

AgION impregnated catheter (N = 45)

AgION silver zeolite-impregnated polyurethane catheter (4.0–5.0 F Lifecath PICC Expert™, Vygon, Ecouen, France). Umbilical vein catheters inserted under sterile conditions after skin disinfection using 2% chlorhexidine. Insertion site covered with a transparent film dressing. Venous lines were changed daily and catheter hubs cleaned with 2% chlorhexidine every time they were assessed

Loss to follow-up	Not reported
% Female	56%
Mean age (SD)	Not reported
Mean gestational age (SD)	26.2 (2.0) weeks

Non-impregnated polyurethane umbilical catheter (N = 41)

Polyurethane catheter (3.5–5.0 F Argyle™, Kendall, Tullamore, Iceland). Umbilical vein catheters inserted under sterile conditions after skin disinfection using 2% chlorhexidine. Insertion site covered with a transparent film dressing. Venous lines were changed daily and catheter hubs cleaned with 2% chlorhexidine every time they were assessed

Loss to follow-up	Not reported
% Female	56%
Mean age (SD)	Not reported
Mean gestational age (SD)	26.2 (1.5) weeks

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information for randomisation)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Low
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result Low
Overall bias and Directness
Risk of bias judgement Moderate (Some concerns) *(No information on randomisation)* *Overall Directness* Partially directly applicable *(Italian based study with different methods of clinical practice to the UK. Infection rates reported are higher than those currently reported in the UK)*

1

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3

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2

Gilbert, 2019

Bibliographic Reference	Gilbert R.; Brown M.; Rainford N.; Donohue C.; Fraser C.; Sinha A.; Dorling J.; Gray J.; McGuire W.; Gamble C.; Sinha A.K.; Oddie S.J.; Wane R.; Hubbard M.; Astles R.; Ewer A.K.; Jackson R.; Ranganna R.; Booth N.; Yajamanyam P.K.; Harvey K.; Aladangady N.; Mathew A.; Pilling E.; Bayliss P.; Maddock N.; Woodhead L.; Chang M.; Dharmaraj S.; Lodge C.; Navarra H.; Roehr C.; Barlow S.; Yadav M.; Abbott C.; Johnson K.; Batra D.; Hooton Y.; Cairns P.; Chapman J.; Sharma B.K.; Smith H.; Ali I.; Lancoma-Malcolm I.; Muller-Pebody B.; Harron K.; Moitt T. ; Antimicrobial-impregnated central venous catheters for prevention of neonatal bloodstream infection (PREVAIL): an open-label, parallel-group, pragmatic, randomised controlled trial; The Lancet Child and Adolescent Health; 2019; vol. 3 (no. 6); 381-390

3 **Study details**

Study type	Randomised controlled trial (RCT)
Study location	England
Study setting	18 neonatal units
Study dates	August 2015 - January 2017
Duration of follow-up	Infection outcomes - 48 hours after PICC removal or after last unsuccessful PICC insertion Secondary outcomes - Until discharged home, death or 6 months after randomisation (whichever occurred first)
Sources of funding	UK National Institute for Health Research Health Technology Assessment (NIHR HTA) programme
Inclusion criteria	Babies requiring a narrow-gauge peripherally inserted CVC French gauge 1 PICC
Exclusion criteria	Known allergy or hypersensitivity to rifampicin or miconazole
Sample size	861
Outcome measures	Neonatal mortality Death before hospital discharge and death within 6 months of randomisation Culture-proven late-onset neonatal infection Finding of one culture of a peripheral, percutaneously-obtained blood sample that was positive for the same organism found to colonize the UVC tip with central line in place or within 48 hours of removal Antimicrobial resistance

	Rifampicin resistance from blood or CSF culture, or from PICC tip culture

1

2 **Study arms**

Antimicrobial-impregnated PICC (N = 430)

Miconazole and rifampicin-impregnated PICC (Premistar; Vygon). Inserted according to standard unit policy and practice)

Loss to follow-up	5
% Female	50%
Mean age (SD) (days)	Median (IQR): 4.12 (2.04–5.93)
Gestational age at birth (weeks)	Median (IQR): 27.9 (25.78-29.94)

Standard PICC (N = 431)

Standard (non-impregnated) PICC (Premicath; Vygon). Inserted according to standard unit policy and practice

Loss to follow-up	3
% Female	48%
Mean age (SD) (days)	Median (IQR): 3.90 (1.90-6.12)
Gestational age at birth (weeks)	Median (IQR): 28.06 (26.23-30.14)

3

4

Klemme, 2020

Bibliographic Reference	Klemme, M.; Staffler, A.; De Maio, N.; Lauseker, M.; Schubert, S.; Innocenti, P.; Wurster, T.M.; Foerster, K.; Herber-Jonat, S.; Mittal, R.; Messner, H.; Flemmer, A.W.; Use of impregnated catheters to decrease colonization rates in neonates - A randomized controlled pilot trial; Journal of Neonatal-Perinatal Medicine; 2020; vol. 13 (no. 2); 231-237

1 **Study details**

Study type	Randomised controlled trial (RCT)
Study location	Germany and Italy
Study setting	Division of Neonatology, Dr. v. Hauner Children's Hospital and Perinatal Center Munich, and Division of Neonatology, Bolzano Central Teaching Hospital, Bolzano
Study dates	January 2014 - December 2015
Duration of follow-up	21 days
Sources of funding	Vygon Inc.
Inclusion criteria	All preterm and term infants who had a clinical indication for a percutaneous inserted central catheter (PICC)
Exclusion criteria	Severe congenital malformations Chromosomal aberrations Immunodeficiency
Sample size	77
Interventions	Miconazole-rifampicin impregnated PICC Standard PICC
Outcome measures	Culture-proven infection

2

3 **Study arms**

Impregnated PICC (N = 41)

PICC which releases rifampicin 98.6ug/d and miconazole 17.4ug/day over a period of up to 21 days (Vygon Premistar®, 28G)

Loss to follow-up	3
% Female	54.1%

Condition specific characteristics	Median gestational age (range) 29+5 weeks (23+2 - 37+0) Median birth weight (range) 960 g (510-2650)

Standard PICC (N = 36)

Non-impregnated PICC (Vygon, Premicath®, 28G)

Split between study groups	36
Loss to follow-up	3
% Female	47.1%
Condition specific characteristics	Median gestational age (range) 27+4 weeks (23+2 - 34+4) Median birth weight (range) 915 g (470 - 2170)

1 **Risk of bias**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes

Section	Question	Answer
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No information
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Probably yes
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Limited information about analysis methods)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no *(Objective outcome)*
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements	No/Probably no

Section	Question	Answer
	(e.g. scales, definitions, time points) within the outcome domain?	
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(Limited information about analysis methods)*
	Overall Directness	Directly applicable

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Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)
Low
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data
Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
Low
Overall Directness
Directly applicable

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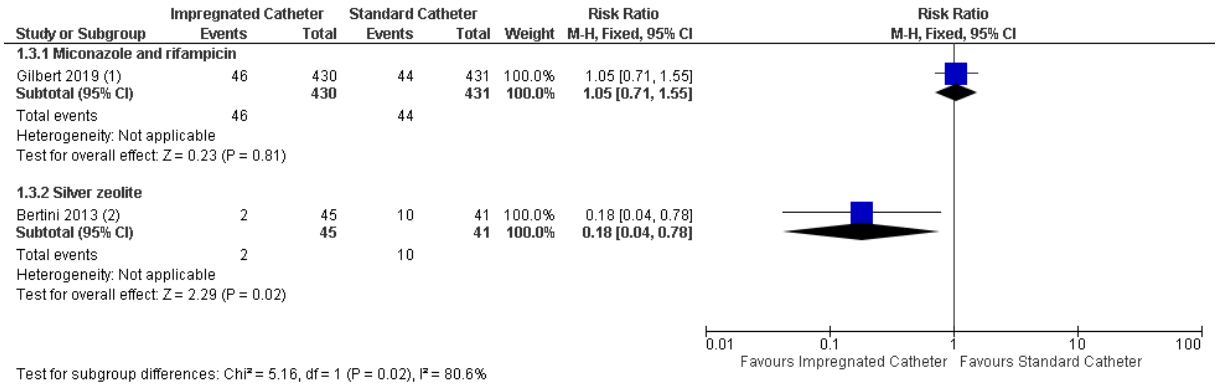
Appendix E – Forest plots

Impregnated catheters (miconazole and rifampicin or silver zeolite) vs standard catheters

Late-onset neonatal infection (culture-confirmed or suspected infection)

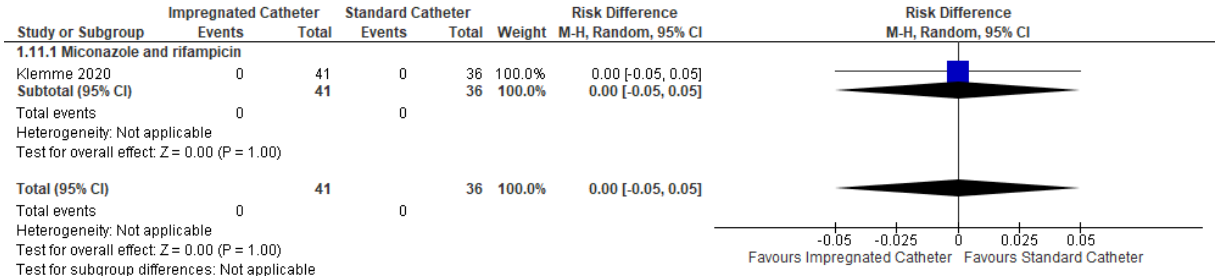


Test for subgroup differences: Chi² = 5.16, df = 1 (P = 0.02), I² = 80.6%

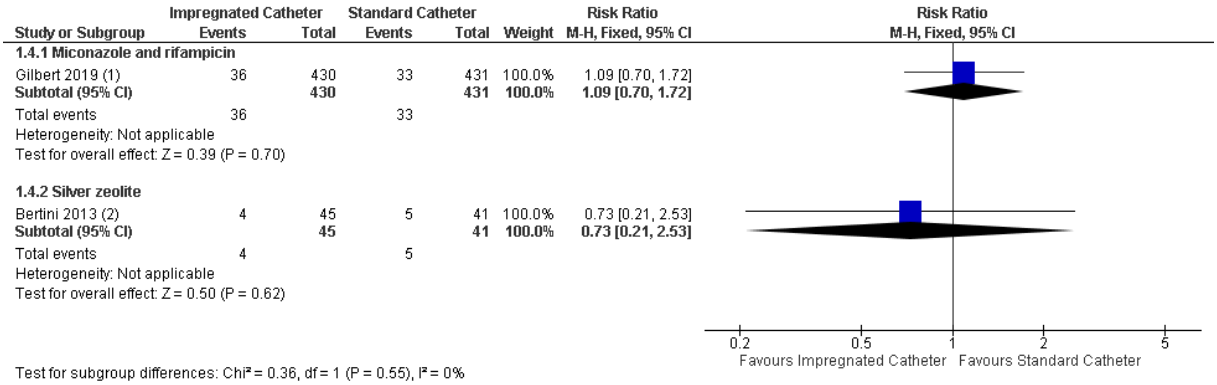
Footnotes

(1) Miconazole and rifampicin-impregnated PICC. Taken from Table 4 (time to first bloodstream infection). Source of infection (e.g. catheter-related or other source not stated)

(2) AgION silver zeolite-impregnated polyurethane catheter. Combined outcome from Table 2 (Definite or probable catheter-related bloodstream infection and bloodstream...



Neonatal mortality (before hospital discharge)



Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55), I² = 0%

Footnotes

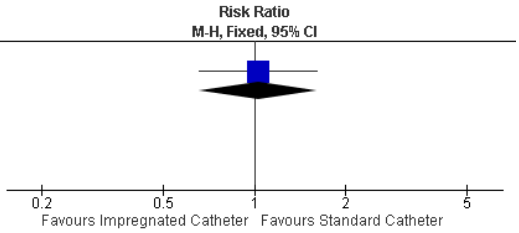
(1) Miconazole and rifampicin-impregnated PICC

(2) AgION silver zeolite-impregnated polyurethane catheter

Neonatal mortality (6 months follow-up)

Study or Subgroup	Impregnated Catheter Events	Total	Standard Catheter Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.2 Miconazole and rifampicin						
Gilbert 2019 (1)	36	430	35	431	100.0%	1.03 [0.66, 1.61]
Subtotal (95% CI)		**430**		**431**	**100.0%**	**1.03 [0.66, 1.61]**
Total events	36		35			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.89)



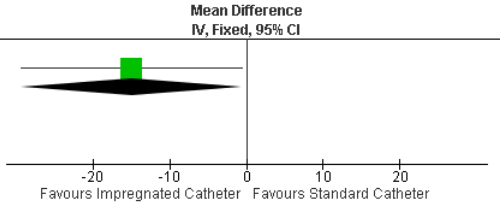
Test for subgroup differences: Not applicable

Footnotes
(1) Miconazole and rifampicin-impregnated PICC

Neonatal length of stay (days)

Study or Subgroup	Impregnated Catheter Mean	SD	Total	Standard Catheter Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.7.1 Silver zeolite								
Bertini 2013	70	33	45	85	35	41	100.0%	-15.00 [-29.41, -0.59]
Subtotal (95% CI)			**45**			**41**	**100.0%**	**-15.00 [-29.41, -0.59]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.04 (P = 0.04)



Test for subgroup differences: Not applicable

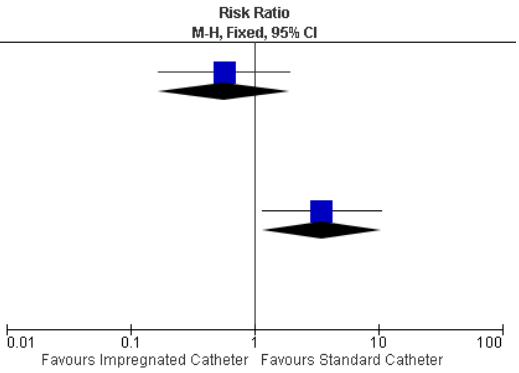
Antimicrobial resistance (miconazole and rifampicin vs standard catheter only)

Study or Subgroup	Impregnated Catheter Events	Total	Standard Catheter Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.9.1 Resistance from blood or CSF culture						
Gilbert 2019 (1)	4	430	7	431	100.0%	0.57 [0.17, 1.94]
Subtotal (95% CI)		**430**		**431**	**100.0%**	**0.57 [0.17, 1.94]**
Total events	4		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)

1.9.2 Resistance from PICC tip culture						
Gilbert 2019 (2)	14	430	4	431	100.0%	3.51 [1.16, 10.57]
Subtotal (95% CI)		**430**		**431**	**100.0%**	**3.51 [1.16, 10.57]**
Total events	14		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.23 (P = 0.03)



Test for subgroup differences: Chi² = 4.66, df = 1 (P = 0.03), I² = 78.5%

Footnotes
(1) Rifampicin resistance
(2) Rifampicin resistance

Appendix F – GRADE tables

As part of the NICE pilot project, the quality of outcomes in intervention reviews was based on risk of bias, inconsistency and indirectness. Imprecision was considered by the committee and is covered in the committee's discussion of the evidence (section 1.1.10), but was not used to downgrade outcome quality. Further information can be found in the guideline methods chapter.

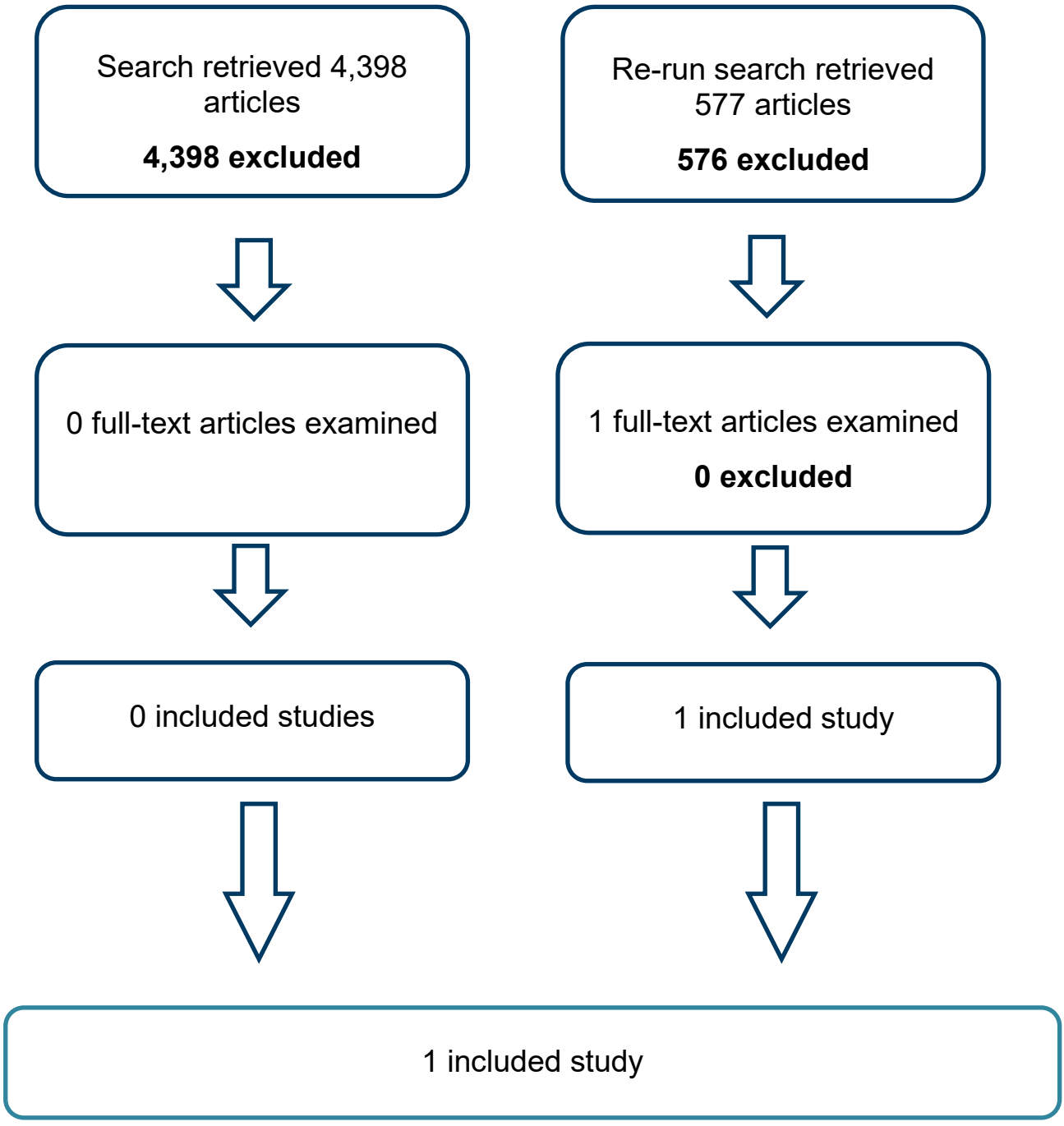
No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Late-onset neonatal infection (RR <1 favours impregnated catheter)									
Antimicrobial subgroup: Miconazole and rifampicin (culture-proven or suspected infection)									
1 (Gilbert 2019)	Parallel RCT	861	RR 1.05 (0.71, 1.55)	10 per 100	11 per 100 (7, 16)	Not serious	N/A	Not serious	High
Antimicrobial subgroup: Miconazole and rifampicin (culture-proven infection)									
1 (Gilbert 2019)	Parallel RCT	77	RD 0.00 (-0.05, 0.05)	-	-	Serious[1]	N/A	Not serious	Moderate
Antimicrobial subgroup: Silver zeolite									
1 (Bertini 2013)	Parallel RCT	86	RR 0.18 (0.04, 0.78)	24 per 100	4 per 100 (1, 19)	Serious$_1$	N/A	Serious$_2$	Low
Neonatal mortality (before hospital discharge) (RR <1 favours impregnated catheter)									
Antimicrobial subgroup: Miconazole and rifampicin									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
1 (Gilbert 2019)	Parallel RCT	861	RR 1.09 (0.70, 1.72)	8 per 100	8 per 100 (5, 13)	Not serious	N/A	Not serious	High
Antimicrobial subgroup: Silver zeolite									
1 (Bertini 2013)	Parallel RCT	86	RR 0.73 (0.21, 2.53)	12 per 100	9 per 100 (3, 31)	Serious[1]	N/A	Serious[2]	Low
Neonatal mortality (6-month follow up) (RR <1 favours impregnated catheter)									
Antimicrobial subgroup: Miconazole and rifampicin									
1 (Gilbert 2019)	Parallel RCT	861	RR 1.03 (0.66, 1.61)	8 per 100	8 per 100 (5, 13)	Not serious	N/A	Not serious	High
Neonatal length of stay (days) (MD <0 favours impregnated catheter)									
Antimicrobial subgroup: Silver zeolite									
1 (Bertini 2013)	Parallel RCT	86	MD -15.00 (-29.41, -0.59)	-	-	Serious[1]	N/A	Serious[2]	Low
Antimicrobial resistance (Resistance from blood or CSF culture) (RR <1 favours impregnated catheter)									
Antimicrobial subgroup: Miconazole and rifampicin									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
1 (Gilbert 2019)	Parallel RCT	861	RR 0.57 (0.17, 1.94)	2 per 100	1 per 100 (0, 3)	Not serious	N/A	Not serious	High
Antimicrobial resistance (Resistance from PICC tip culture) (RR <1 favours impregnated catheter)									
Antimicrobial subgroup: Miconazole and rifampicin									
1 (Gilbert 2019)	Parallel RCT	861	RR 3.51 (1.16, 10.57)	1 per 100	3 per 100 (1, 10)	Not serious	N/A	Not serious	High

1. Single study at moderate risk of bias. Downgraded 1 level
2. Single study which is partially directly applicable. Downgraded 1 level

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

Grosso et al (2020). Cost-effectiveness of strategies preventing late-onset infection in preterm infants

Study details	**Analysis:** Cost utility analysis **Approach to analysis:** Excel based model to estimate the direct cost and effectiveness (QALYs) associated with LOI for a lifetime horizon. **LOI related complications considered:** No NDI, mild NDI, moderate NDI, severe NDI **Perspective:** UK NHS **Time horizon:** Lifetime **Discounting:** 3.5%
Interventions	**Analysis 1: Gestational age (weeks) 23-27** **Intervention 1:** S-PICCs **Intervention 2:** AM-PICCs **Analysis 2: Gestational age (weeks) 28-32** **Intervention 1:** S-PICCs **Intervention 2:** AM-PICCs
Population	**Population:** Infants born ≤32 weeks gestational age who required a PICC during their NICU stay
Data sources	**Effectiveness:** Effect of Am-PICC on the probability of LOI came from the PREVAIL trial. **Costs:** Difference in costs between S-PICCs and AM-PICCs obtained via personal communication from the manufacturer. Healthcare costs between PICC insertion and 6 months came from the PREVAIL trial and linked datasets (NNRD, PICANet and HES), and costs between 6 months and 2 years came from NHS reference costs for 2015/2016 derived from HES inpatient, A&E and outpatient data. Annual costs between age 2 and 10 by NDI category came from Petrou et al 2009 and inflated to 2016 values. Annual costs after age 11 came from Petrou et al 2013 and inflated to 2016 values. **QoL:** QoL associated by NDI level taken from Petrou et al 2013. These scores were applied directly and were not adjusted by age.
Base-case results	**2016 UK pounds sterling**

Analysis	Insulin	Absolute		Incremental		
		Costs (£)	QALYs	Costs (£)	QALYs	Net health benefit at £20,000/QALY
Analysis 1	S-PICCs	127,128	16.49			
	AM-PICCs	127,183	16.48	55	-0.01	-0.01
Analysis 2	S-PICCs	83,533	21.46			
	AM-PICCs	83,588	21.46	55	0.00	-0.01

Sensitivity analyses	**Deterministic:** Sensitivity analysis showed that the base case results of the model were robust to all parameters except the relative risk of infection with AM-PICCs and the effect of LOI on the risk of death. If AM-PICCs successfully reduce the risk of LOI they would have a positive net health benefit. **Probabilistic:** No probabilistic sensitivity analysis was conducted.
Comments	**Source of funding:** National institute for health Research (NIHR)-Health Technology Assessment (HTA) Programme **Limitations:** Minor limitations

Abbreviations: AM-PICCs, antimicrobial impregnated PICCs; HES, hospital episode statistics; LOI, late onset infection; NDI, neurodevelopmental impairment; NHS, National Health Service; NNRD, national neonatal research database; PICANet, Paediatric intensive care network; QALYs, quality-adjusted life years; S-PICCs, standard non-impregnated PICCs; UK, United Kingdom

Applicability checklist

Study	1.1 Is the study population appropriate for the review question?	1.2 Are the interventions appropriate for the review question?	1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	1.4 Is the perspective for costs appropriate for the review question?	1.5 Is the perspective for outcomes appropriate for the review question?	1.6 Are all future costs and outcomes discounted appropriately?	1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome?	1.8 Overall judgement
Grosso et al (2020)	Yes	Yes	Yes	Yes	Yes	Yes	No (Health Utilities Index mark 3 at age 11 from parents of infants)	Partially applicable

Limitations checklist

Study	2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	2.3 Are all important and relevant outcomes included?	2.4 Are the estimates of baseline outcomes from the best available source?	2.5 Are the estimates of relative intervention effects from the best available source?	2.6 Are all important and relevant costs included?	2.7 Are the estimates of resource use from the best available source?	2.8 Are the unit costs of resources from the best available source?	2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	2.11 Has no potential financial conflict of interest been declared?	2.12 Overall assessment
Grosso et al (2020)	Yes	Yes	Yes	Yes	Yes	Partly (sourced from clinical trial)	Partly (sourced from manufacturer)	Partly (annual costs of NDI sourced from published paper)	Yes	Partly (PSA not performed)	No	Potentially serious limitations

Appendix I – Health economic model

This question was not prioritised for original economic analysis.

1 Appendix J – Excluded studies

2 Clinical studies

Study	Reason for exclusion
Alcock, Gary, Liley, Helen G, Cooke, Lucy et al. (2017) Prevention of neonatal late-onset sepsis: a randomised controlled trial.. BMC pediatrics 17(1): 98	- Study does not contain a relevant intervention
Balain Munisha, Oddie Sam, McGuire William (2014) Antimicrobial-impregnated central venous catheters for prevention of catheter-related bloodstream infection in newborn infants. Cochrane Database of Systematic Reviews: Reviews issue5	- Systematic review protocol
Balain, Munisha; Oddie, Sam J; McGuire, William (2015) Antimicrobial-impregnated central venous catheters for prevention of catheter-related bloodstream infection in newborn infants.. The Cochrane database of systematic reviews: cd011078	- Systematic review not used as a source of primary studies
Cox E.G., Knoderer C.A., Jennings A. et al. (2013) A randomized, controlled trial of catheter-related infectious event rates using antibiotic-impregnated catheters versus conventional catheters in pediatric cardiovascular surgery patients. Journal of the Pediatric Infectious Diseases Society 2(1): 67-70	- Does not contain the correct population *[Children but not newborn babies up to 28 days]*
Gilad J. and Borer A. (2006) Prevention of catheter-related bloodstream infections in the neonatal intensive care setting. Expert Review of Anti-Infective Therapy 4(5): 861-873	- Review article but not a systematic review
Gilbert, Ruth E and Harden, Melissa (2008) Effectiveness of impregnated central venous catheters for catheter related blood stream infection: a systematic review.. Current opinion in infectious diseases 21(3): 235-45	- Systematic review that does not contain the relevant population
Kulali F., Calkavur S., Oruc Y. et al. (2019) Impact of central line bundle for prevention of umbilical catheter-related bloodstream infections in a neonatal intensive care unit: A pre-post intervention study. American Journal of Infection Control 47(4): 387-390	- Study does not contain a relevant intervention
Payne, Victoria, Hall, Mike, Prieto, Jacqui et al. (2018) Care bundles to reduce central line-associated bloodstream infections in the neonatal unit: a systematic review and meta-analysis.. Archives of disease in childhood. Fetal and neonatal edition 103(5): f422-f429	- Systematic review that does not contain a relevant intervention
Smulders CA, van Gestel JP, Bos AP (2013) Are central line bundles and ventilator bundles effective in critically ill neonates and children?. Intensive Care Medicine 39(8): 1352-1358	- Systematic review that does not contain a relevant intervention
Takashima, Mari, Ray-Barruel, Gillian, Ullman, Amanda et al. (2017) Randomized controlled trials in central vascular access devices: A scoping review.. PloS one 12(3): e0174164	- Systematic review that does not contain a relevant intervention
Weber D.J., Brown V.M., Sickbert-Bennett E.E. et al. (2010) Sustained and prolonged reduction in central line-associated bloodstream infections as a result of multiple interventions. Infection Control and Hospital Epidemiology 31(8): 875-877	- Review article but not a systematic review

Economic studies

No studies were excluded at full-text review.

Appendix K – Research recommendations – full details

K.1 Research recommendation

What is the effectiveness of antimicrobial-impregnated catheters other than those impregnated with rifampicin and miconazole for preventing neonatal catheter-related bloodstream infections in newborn babies?

K.2 Why this is important

Three RCTs were identified for the effectiveness of antimicrobial-impregnated catheters for preventing catheter-related bloodstream infections in newborn babies. These evaluated the use of a miconazole and rifampicin impregnated peripherally inserted central catheter and a silver zeolite impregnated umbilical vein catheter. Two of the studies had small sample sizes and evidence varied from high to low quality, with a high degree of uncertainty in the outcomes. There is currently no evidence for other types of catheters or other antimicrobials, making it difficult to establish how effective the use of impregnated catheters are for reducing neonatal infection.

Further research is needed using a robust study design such as a parallel RCT to establish whether antimicrobial impregnated catheters can have benefits for the treatment of newborn babies compared to the use of standard, non-impregnated catheters. Studies should be UK based and consider the effects on newborn babies, both term and pre-term. Research in this area is essential to determine whether the use of antimicrobial impregnated catheters can be recommended in the future to help improve patient outcomes.

K.3 Rationale for research recommendation

Importance to ‘patients’ or the population	Intravascular catheters are commonly used in neonatal care for the delivery of fluids and medication to the neonate. However, catheters are also associated with the development of bloodstream infection. The use of antimicrobial-impregnated intravascular catheters may therefore help to reduce the risk of late-onset neonatal infection. If research establishes that antimicrobial-impregnated catheters are effective, then their use may help to reduce the number of babies who develop neonatal infection and experience the various harms associated with infection.
Relevance to NICE guidance	Due to limited evidence the committee were not able to make recommendations in favour of the use of antimicrobial-impregnated catheters. Future research will help to determine whether antimicrobial-impregnated catheters should be

	recommended as a way to reduce a baby's risk of developing neonatal infection.
Relevance to the NHS	The outcome would determine whether babies would benefit from the use of antimicrobial-impregnated catheters over standard catheters to reduce their risk of developing an infection. Reducing the number of babies who require treatment for catheter-associated infection will also reduce costs to the NHS and reduce hospital length of stay..
National priorities	Medium
Current evidence base	This review identified 3 studies, some of which had small sample sizes, and reported low quality evidence. Data was reported for neonatal outcomes when babies were given standard or antimicrobial-impregnated catheters.
Equality considerations	No specific equality concerns are relevant to this research recommendation.

K.12 Modified PICO table

PICO	**Population:** Newborn babies with central venous catheters **Interventions:** Catheters impregnated with a combination of antimicrobials other than miconazole and rifampicin **Comparator:** Non-impregnated catheter **Outcomes:** Culture proven bloodstream infection Length of stay Mortality
Current evidence base	3 RCTs
Study design	Randomised controlled trial
Other comments	Study should be adequately powered, include an adequate follow-up period, and should collect data on resource-use and cost

K.13 Research recommendation

What is the effectiveness of catheters impregnated with silver zeolite for preventing neonatal catheter-related bloodstream infections in newborn babies?

K.14 Why this is important

One RCT was identified for the effectiveness of silver zeolite impregnated catheters for preventing catheter-related bloodstream infections in newborn babies. This study evaluated the use of a silver zeolite impregnated umbilical vein catheter, indicating

that their use can reduce the number of newborn babies developing late-onset neonatal infection. This study had a small sample size and reported low quality outcomes with a high degree of uncertainty in the results. There is currently no other research that has evaluated the use of silver zeolite in catheters, either to validate these findings or to examine the effectiveness of silver zeolite in other types of catheter.

Further research is needed using a robust study design such as a parallel RCT to establish whether silver zeolite impregnated catheters can have benefits for the treatment of newborn babies compared to the use of standard, non-impregnated catheters. Studies should be UK based and consider the effects on newborn babies, both term and pre-term. Research in this area is essential to determine whether the use of silver zeolite impregnated catheters can be recommended in the future to help improve patient outcomes.

K.143 Rationale for research recommendation

Importance to 'patients' or the population	Intravascular catheters are commonly used in neonatal care for the delivery of fluids and medication to the neonate. However, catheters are also associated with the development of bloodstream infection. The use of antimicrobial-impregnated intravascular catheters may therefore help to reduce the risk of late-onset neonatal infection. If research establishes that silver zeolite-impregnated catheters are effective, then their use may help to reduce the number of babies who develop neonatal infection and experience the various harms associated with infection.
Relevance to NICE guidance	Due to limited evidence the committee were not able to make recommendations in favour of the use of silver zeolite-impregnated catheters. Future research will help to determine whether silver zeolite-impregnated catheters should be recommended as a way to reduce a baby's risk of developing neonatal infection.
Relevance to the NHS	The outcome would determine whether babies would benefit from the use of silver zeolite-impregnated catheters over standard catheters to reduce their risk of developing an infection. Reducing the number of babies who require treatment for catheter-associated infection will also reduce costs to the NHS and reduce hospital length of stay..
National priorities	Medium
Current evidence base	This review identified 1 study, with a small sample size and low quality outcomes. The study reported data on neonatal outcomes when

	babies were given standard or silver zeolite-impregnated catheters.
Equality considerations	No specific equality concerns are relevant to this research recommendation.

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K.134 Modified PICO table

PICO	**Population:** Newborn babies with central venous catheters **Interventions:** Catheters impregnated with silver zeolite **Comparator:** Non-impregnated catheter **Outcomes:** Culture proven bloodstream infection Length of stay Mortality
Current evidence base	1 RCT
Study design	Randomised controlled trial
Other comments	Study should be adequately powered, include an adequate follow-up period, and should collect data on resource-use and cost

4