National Institute for Health and Care Excellence

Draft

Neonatal infection: antibiotics for prevention and treatment

Evidence reviews for antifungal prophylaxis for treating late-onset neonatal infection

NICE guideline <number>

Evidence reviews underpinning recommendations 1.14.1-1.14.2 in the NICE guideline

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Draft for Consultation

These evidence reviews were developed by NICE Guideline Updates Team

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ISBN:

Contents

Antifungal prophylaxis for late-onset neonatal infection

1.1 Review question

What is the clinical and cost effectiveness of starting prophylactic antifungal treatment when starting antibiotic treatment for suspected 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.

Prophylactic antifungals can also be given to the baby when antibiotics are given for suspected neonatal infection. There are a range of different antifungals that can be given to a baby to help prevent fungal infection. Establishing the effectiveness of these treatments are important to help to reduce the harms associated with infection. The aim of this review is to establish the clinical and cost-effectiveness of antifungals for preventing the development of neonatal fungal infection.

1.1.2 Summary of the protocol

Table 1 PICO table

Population	• Babies receiving antibiotic treatment for suspected late-onset neonatal bacterial infection
Interventions	• Antifungal prophylaxis treatments used alongside antibiotic treatment for neonatal infection, such as: • amphotericin B deoxycholate • fluconazole • micafungin • nystatin Antifungals will not be grouped by class for the purpose of the analysis.
Comparator	• Head-to-head comparison with any of the interventions, including comparison of different treatment durations and doses • Placebo • No treatment / usual care
Outcomes	Neonatal outcomes • Culture-proven invasive fungal 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

	• Mortality (during the neonatal period at the latest time point reported in the study) • Length of hospital stay • Adverse drug reactions specifically related to antifungals) • Neurodevelopmental outcomes (measured using a validated tool at the latest time point reported in the study) • Antifungal resistance (culture proven) Family outcomes • psychological distress in baby's family as measured using a validated scale (e.g. parental stressor scale NICU; modified Rutter Malaise Inventory) (during the neonatal period and at the latest timepoint reported in study)

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 used in 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. No studies were found that matched the inclusion criteria for the review. However, some were found which examined the effectiveness of antifungal prophylaxis in preterm and very low birthweight babies. The committee decided that this population could provide indirect evidence that could inform this review question and so studies that examined this population were included in the review. All outcomes were downgraded for indirectness to reflect the indirect nature of the evidence in the GRADE profile. A supplementary search was conducted to identify studies which included this population. For the modified population of preterm and low birthweight babies, 2 systematic reviews were identified which were fully applicable to the review question (Austin 2015, Cleminson 2015). These reviews were assessed for quality using the ROBIS checklist and were judged to be high quality (Appendix D). The reviews were therefore used as a source of data for this review question. Studies identified by these systematic reviews were included and supplemented with additional studies identified in the search. Data and risk of bias judgements were extracted directly from the systematic reviews rather than the original studies.

The included studies (for details see section 1.1.4) compared a range of antifungals, either against other antifungals, placebo or control. Most studies reported the incidence of invasive fungal infection and a number of studies also reported mortality and length of stay. No information was found for family outcomes. These results were analysed using a network meta-analysis (for full NMA methods, see the methods document and Appendix L). The studies that examined the use of fluconazole used a range of doses and so the fit of the NMA model was compared when doses were analysed as a group or by separating into higher and lower dose groups. Separating the fluconazole doses did not improve the model fit and so the different dose groups were combined in the analyses. All other outcomes were analysed using pairwise meta-analyses. For consistency, results of the pairwise meta-analyses were reported as odds ratios, to match the statistical outputs from the NMA. This enabled comparisons between the pairwise and NMA results in the relative effectiveness tables.

Where observational studies were included for antifungal resistance outcomes (for details see section 1.1.4), only those that used a comparative observational design were included. Studies that used a non-comparative design were excluded from the review.

This review did not use imprecision as part of the quality assessment of outcome measures (see the methods document for details). 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 (or credible) intervals comparing those treatments crossed the line of no effect. If the confidence interval did not cross the line of no effect, the direction of the effect is indicated. The imprecision associated with a particular outcome and more detailed discussions of the effects are described in the committee's discussion of the evidence.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Initially, a combined search for this review and the review on antibiotics for late-onset neonatal infection returned a total of 4896 results. Of these, 118 were identified as potential includes for either question, with full text articles ordered and reviewed against the inclusion criteria. No studies met the inclusion criteria for this review.

An additional search for articles investigating the effectiveness of antifungals for preterm and low birthweight babies returned a total of 648 results. Of these, 41 were identified as potential includes, and full text articles were ordered and reviewed against the inclusion criteria. For the modified population of preterm and low birthweight babies, 2 systematic reviews were identified which were fully applicable to the review question (Austin 2015, Cleminson 2015). These reviews were assessed for quality using the ROBIS checklist and were judged to be high quality. The reviews were therefore used as a source of data for this review question, and 13 RCTs from these reviews were included. Four additional studies met the inclusion criteria for this review, 1 RCT and 3 observational studies.

Both searches were re-run in July 2020 to identify any studies which had been published since the date of the original search. The additional search returned a total of 41 results of which 5 were identified as possible included studies. After full text review, 1 RCT met the inclusion criteria. In total there were therefore 18 studies which met the inclusion criteria for this review, 15 parallel RCTs and 3 comparative observational studies.

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	Follow-up time	Population	Intervention	Comparator	Outcomes
Randomised controlled trials					
Aydemir 2011 (n=187) Turkey	• 30 days after birth (45 days for extremely low birthweight)	• Very low birthweight infants	Fluconazole *3 mg/kg* Or Nystatin	Placebo Or Nystatin *100,000 U/ml every 8 hours*	• Invasive fungal infection • Mortality

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
			100,000 U/ml every 8 hours Given every 3rd day		
Benjamin 2014 (n=361) USA	• Until 6 weeks after birth	• Birthweight <750 g • <120 hours of age	Fluconazole *6 mg/kg twice weekly for first 6 weeks of life*	Placebo	• Invasive fungal infection • Mortality • Neurodevelopmental impairment • Adverse events (deafness)
Jannatdoust 2015 (n=93) Iran	• Duration of hospitalisation	• Premature infants *<32 weeks gestational age* • Birth weight <1250 g	Fluconazole *6-week treatment with 3 mg/kg dose of fluconazole every 3 days in the first 2 weeks, every 2 days in second 2 weeks and every day in the third 2 weeks*	No treatment	• Length of hospital stay • Mortality
Kaufman 2001 (n=100) USA	• Six weeks or until IV access discontinued	• Extremely low birthweight infants • <5 days old	Fluconazole *3 mg/kg every 3rd day for 2 weeks then every 2nd day for 2 weeks, then daily for final 2 weeks*	Placebo	• Invasive fungal infection • Mortality • Neurodevelopmental outcomes
Kaufman 2005 (n=81)	• Six weeks or until IV access discontinued	• Extremely low birthweight infants • <5 days old • Endotracheal tube or	Fluconazole *3 mg/kg every 3rd day for 2 weeks then every 2nd day for 2*	Fluconazole *3 mg/kg twice weekly for 6 weeks*	• Invasive fungal infection • Mortality

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		central line in situ	*weeks, then daily for final 2 weeks*		
Kicklighter 2001 (n=103) USA	• Four weeks	• Very low birthweight infants • <3 days of age	Fluconazole *6 mg/kg every 3rd day for 1 week then daily for 3 weeks*	Placebo	• Invasive fungal infection • Mortality
Kirpal 2015 (n=80) India	• 28 days or discharge (whichever was sooner)	• Very low birthweight • Receiving antibiotics >3 days	Fluconazole *Every other day for 7 days then every day until 28 days or discharge*	Placebo	• Invasive fungal infection • Mortality
Manzoni 2007 (n=322) Italy	• 30 days after birth (45 days for extremely low birthweight)	• Very low birthweight infants	Fluconazole *3 mg/kg or 6 mg/kg every 2nd day for 30 days*	Placebo	• Invasive fungal infection • Mortality
Mersal 2013 (n=59) Saudi Arabia	• Until 6 weeks after birth	• Preterm infants *<30 weeks* • Birthweight <1200 g	Fluconazole *6 mg/kg every 72 hours for 1st week then every 48 hours until 6th week after birth*	Nystatin *100,000 IU every 8 hours for 6 weeks*	• Invasive fungal infection • Mortality
Parikh 2007 (n=121) India	• Until 4 weeks after birth	• Very low birthweight infants • <3 days of age	Fluconazole *6 mg/kg every 3rd day for 1 week then every day until 4 weeks*	Placebo	• Invasive fungal infection • Mortality

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
Ozturk 2006 (n=349) Turkey	• Not reported	• Very low birthweight infants	Nystatin *1000,000 IU every 8 hours*	No treatment	• Invasive fungal infection • Mortality
Rundjan 2020 (n=95) Indonesia	• Duration of antifungal treatment	• Admitted to the neonatal intensive care unit within the first 72 h of life • Gestational age of ≤ 32 weeks • Birth weight ≤ 1500 g	Nystatin *100,000 U/ml (1 ml dose) 3 times per day for 6 weeks or until no fungal infection risk factors were noted*	Control *1 ml sterile water, 3 times per day*	• Invasive fungal infection • Mortality
Sims 1988 (n=67) USA	• Not reported	• Birth weight <1250 g	Nystatin *1 ml every 8 hours*	No treatment	• Invasive fungal infection • Mortality • Length of hospital stay
Violaris 2010 (n=80) USA	• Until full oral feeding achieved, or systemic fungal infection diagnosed	• Very low birthweight infants	Fluconazole *4 mg/kg once per day from day 5 after birth until full oral feeding achieved or fungal infection diagnosed*	Nystatin *100,000 units/kg/day from day 5 after birth until full oral feeding achieved or fungal infection diagnosed*	• Invasive fungal infection • Mortality
Wainer 1992 (n=600) South Africa	• Not reported	• Birth weight <1750 g	Miconazole *0.75 ml 3 times per day*	Placebo	• Invasive fungal infection • Mortality • Length of hospital stay
Observational studies					
Lee 2016 (n=423) Korea	• Duration of hospitalisation	• Extremely low birthweight	Fluconazole *3 mg/kg fluconazole administered once a day, starting on the 3rd postnatal*	No treatment	• Antifungal resistance

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
			day, twice a week for 4 weeks.		
Manzoni 2006 (n=465) Italy	• 30 days (45 days for extremely low birthweight infants)	• Survived longer than 3 days	Fluconazole *6 mg/kg fluconazole every 72 hours in the first week of life, then every 48 hours from the second week until 30 days of life for neonates with birth weight 1000- 1500 g, 45 days of life for ELBW neonates, or until earlier discharge, or the need for systemic antifungal therapy*	No treatment	• Antifungal resistance
Manzoni 2008 (n=719) Italy	• Duration of hospitalisation	• Survived longer than 3 days	Fluconazole *6 mg/kg fluconazole every 72 hours in the first week of life, then every 48 hours from the second week until 30 days of life for neonates with birth weight 1000- 1500 g, 45 days of life for ELBW*	No treatment	• Antifungal resistance

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
			neonates, or until earlier discharge, or the need for systemic antifungal therapy		

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Summary estimates from network meta-analysis are presented when available. Summary pairwise estimates are only presented for outcomes for which network meta-analysis was not performed.

Table 3 Results and quality assessment of clinical studies included in the evidence review (results of network meta-analysis).

Treatment	OR (95% CrI)	Quality	Interpretation of effect
Invasive fungal infection			
Fluconazole v placebo	0.26 (0.12, 0.54)	Very low	Favours fluconazole
Nystatin v placebo	0.19 (0.07, 0.59)		Favours nystatin
Miconazole v placebo	1.34 (0.17, 10.67)		Could not differentiate
Nystatin v fluconazole	0.73 (0.25, 2.59)		Could not differentiate
Miconazole v fluconazole	5.16 (0.60, 47.98)		Could not differentiate
Nystatin v miconazole	0.14 (0.02, 1.52)		Could not differentiate
Mortality (all cause mortality)			
Fluconazole v placebo	0.72 (0.53, 0.95)	Very low	Favours fluconazole
Nystatin v placebo	0.90 (0.61, 1.34)		Could not differentiate
Miconazole v placebo	0.80 (0.58, 1.12)		Could not differentiate
Nystatin v fluconazole	1.26 (0.79, 2.02)		Could not differentiate
Miconazole v fluconazole	1.12 (0.72, 1.75)		Could not differentiate
Nystatin v miconazole	1.13 (0.67, 1.91)		Could not differentiate
Length of stay			
Fluconazole v placebo	-0.14 (-3.79, 3.48)	Very low	Could not differentiate
Nystatin v placebo	-0.96 (-6.43, 4.47)		Could not differentiate
Miconazole v placebo	-0.30 (-5.03, 4.51)		Could not differentiate
Nystatin v fluconazole	-0.81 (-8.27, 4.61)		Could not differentiate
Miconazole v fluconazole	-0.14 (-6.06, 5.84)		Could not differentiate
Nystatin v miconazole	-0.63 (-7.97, 6.56)		Could not differentiate

Table 4 Results and quality assessment of clinical studies included in the evidence review (results of pair-wise meta-analysis for outcomes where network meta-analysis was not performed)

Comparison	No. studies	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Fluconazole v placebo/no treatment					
Neurodevelopmental outcomes					
Communication	1	38	MD 2.00 (-6.71, 10.71)	Low	Could not differentiate
Daily living skills	1	38	MD 0.50 (-5.83, 6.83)	Low	Could not differentiate
Socialisation	1	38	MD 2.80 (-2.64, 8.24)	Low	Could not differentiate
Motor skills	1	38	MD -3.00 (-13.30, 7.30)	Low	Could not differentiate
Neurodevelopmental impairment (composite score)					
	1	171	OR 1.19 (0.62, 2.31)	Low	Could not differentiate
Drug-related adverse events (deafness)					
	1	185	OR 1.61 (0.37, 6.95)	Low	Could not differentiate
Antifungal resistance					
	3	1213	OR 1.24 (0.70, 2.19)	Very low	Could not differentiate
Fluconazole (escalating dose) v Fluconazole (constant dose)					
Mortality	1	81	OR 0.87 (0.29, 3.31)	Low	Could not differentiate
Fluconazole (3 mg/kg every 2nd day) v Fluconazole (6 mg/Kg every 2nd day)					
Invasive fungal infection	1	216	OR 1.45 (0.32, 6.65)	Low	Could not differentiate
Mortality	1	216	OR 1.08 (0.41,2.85)	Low	Could not differentiate

See appendix E for forest plots and appendix F for full GRADE tables. See appendix K for the full results of the network meta-analysis.

1.1.7 Published 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, 4,385 of the studies could confidently be excluded for this question. 13 studies were excluded following the full-text 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 577 results. Based on title and abstract screening, all the studies could confidently be excluded for this question. Thus, the review for this question does not include any study from the existing literature.

1.1.7.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

1.1.8 Economic model

The committee prioritised this question for original modelling. Table 5 provides a brief summary of methods and results. Appendix I provides full details.

1.1.9 Summary of economic evidence

Table 5: Summary of economic evidence

Methods, applicability and limitations	Base-case results						Uncertainty
	Intervention	Absolute		Incremental			
		Cost (£)	Effects	Cost (£)	Effects	ICER	
Original model developed for this guideline (see Appendix I) 1 decision tree to compare the benefits, harms and costs of giving versus not giving antifungals prophylactically in neonates receiving antibiotics for suspected late onset infection. **Effects:** NMA of RCTs as reported in this review **Costs:** Resource use extrapolated from Schroeder et al. (2009). Long-term morbidity from Mangham et al. (2009) and Petrou et al. (2013). Unit cost from NHS RefCosts (UK) **Utilities:** Long-term morbidity from Petrou et al. (2013). **Directly applicable** with **minor limitations**	**23 weeks' gestation**						
	With broad-spectrum antibiotics						**Deterministic:** Regardless of BSA, not sensitive to any 1 parameter: prophylaxis always retains positive net health benefit compared with none. **Probabilistic:** With BSA: 80.5% probability that nystatin is optimal, 19.5% fluconazole is, and 0% no prophylaxis is at a value of £20K/QALY. Without BSA: 78.7% probability that nystatin is optimal, 21.3% fluconazole is, and 0% no prophylaxis is at a value of £20K/QALY
	Nystatin	£30,761	9.2448				
	Fluconazole	£30,974	9.1850	£212	−0.05980	dominated	
	None	£32,363	8.7492	£1,602	−0.49561	dominated	
	Without broad-spectrum antibiotics						
	Nystatin	£30,583	9.2995				
	Fluconazole	£30,702	9.2683	£119	−0.03120	dominated	
	None	£31,457	9.0272	£874	−0.27232	dominated	
	28 weeks' gestation						
	With broad-spectrum antibiotics						**Deterministic:** Regardless of BSA, not sensitive to any 1 parameter: prophylaxis always retains positive net health benefit compared with none. Fluconazole is preferred to nystatin if either nystatin is less effective or fluconazole is more effective vs placebo in preventing candidiasis. **Probabilistic:** With BSA: 82.1% probability that nystatin is optimal, 17.9% fluconazole is, and 0% no prophylaxis is at a value of £20K/QALY. Without BSA: 84.2% probability that nystatin is optimal, 15.8% fluconazole is, and 0% no prophylaxis is at a value of £20K/QALY
	Nystatin	£25,696	22.2582				
	Fluconazole	£25,759	22.2552	£63	−0.00307	dominated	
	None	£26,098	22.2301	£401	−0.02814	dominated	
	Without broad-spectrum antibiotics						
	Nystatin	£25,656	22.2610				
	Fluconazole	£25,696	22.2594	£40	−0.00156	dominated	
	None	£25,854	22.2467	£198	−0.01432	dominated	

Methods, applicability and limitations	Base-case results						Uncertainty
	Intervention	Absolute		Incremental			
		Cost (£)	Effects	Cost (£)	Effects	ICER	
	33 weeks' gestation						
	With broad-spectrum antibiotics						**Deterministic:** With BSA, model is sensitive to relationship between gestational age and probability of candidiasis. All other parameters continue to see positive net health benefit with nystatin. Without BSA, model is also sensitive to costs of candidiasis. **Probabilistic:** With BSA: 94% probability that nystatin is optimal, 4.7% no prophylaxis is, and 1.3% fluconazole is at a value of £20K/QALY. Without BSA: 73.6% probability that nystatin is optimal, 26.2% no prophylaxis is, and 0.2% fluconazole is at a value of £20K/QALY
	Nystatin	£7,168	24.4010				
	None	£7,180	24.4003	£12	−0.00073	dominated	
	Fluconazole	£7,188	24.4009	£20	−0.00008	dominated	
	Without broad-spectrum antibiotics						
	None	£7,165	24.4007				
	Nystatin	£7,166	24.4011	£0	0.00037	£1,264	
	Fluconazole	£7,185	24.4010	£19	−0.00004	dominated	
	38 weeks' gestation						
	With broad-spectrum antibiotics						**Deterministic:** Regardless of BSA, not sensitive to any 1 parameter: no prophylaxis always preferred. **Probabilistic:** With BSA 97.4% probability that no prophylaxis is optimal at a value of £20K/QALY. Without BSA 99.6%.
	None	£1,674	24.9623				
	Nystatin	£1,686	24.9623	£12	0.00001	£911,752	
	Fluconazole	£1,703	24.9623	£18	0.00000	dominated	
	Without broad-spectrum antibiotics						
	None	£1,673	24.9623				
	Nystatin	£1,686	24.9623	£12	0.00001	£1,927,997	
	Fluconazole	£1,703	24.9623	£17	0.00000	dominated	

BSA = broad-spectrum antibiotics

1

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

The committee discussed how the consequences of a baby developing invasive fungal infection can be very serious, including death and long-term disability. The number of babies developing a fungal infection was therefore considered important, as was mortality. However, as the evidence reported all-cause mortality rather than deaths resulting from fungal infection, the committee decided to prioritise incidence of fungal infection over the evidence for mortality. The committee also thought that evidence on antifungal resistance was very important because antifungal resistance has risen in the last 5 years and it is important to take steps to reduce the development of resistance to avoid future fungal infections becoming more difficult to treat. The committee was also interested in other outcomes, such as neurodevelopmental outcomes and distress in the baby's family, but there was little evidence available for these.

1.1.10.2 The quality of the evidence

There was no evidence that met the inclusion criteria for the population in this review (babies given antifungals when starting antibiotic treatment for late-onset infection). Instead, there was evidence on preterm or low birthweight babies who were given antifungal prophylaxis, but not necessarily also given antibiotics. The committee decided that the effects of antifungals in this group of babies are likely to be similar to those who are given antifungal prophylaxis when starting antibiotics, as many of the babies who develop suspected late-onset neonatal infection will be preterm. Given the differences in population, these studies were graded as indirectly applicable to the review, but the committee used a combination of the evidence and their clinical knowledge and experience to make recommendations specifically for babies who are being given antibiotics for suspected late-onset infection.

For the indirect evidence, there were 15 RCTs and 3 observational studies which investigated the effectiveness of antifungal prophylaxis for preterm or low birthweight babies. Most of the evidence compared the effectiveness of fluconazole or nystatin against placebo, while one study examined the effectiveness of miconazole in comparison to placebo. All outcomes were low- to very low-quality, largely because the population was not directly applicable to the review. Other reasons for downgrading included inconsistency across studies and methodological issues which meant some of the studies were at high risk of bias.

There was sufficient evidence to combine the data into a network meta-analysis (NMA) for the outcomes of invasive fungal infection, mortality and length of stay. There was limited evidence for other outcomes, which either compared fluconazole against placebo or made comparisons between different fluconazole doses. Each of these additional outcomes was based on evidence from a single study meaning that meta-analysis was not possible. Instead, these outcomes were presented as individual study results.

The evidence for fluconazole used a wide range of doses, time between doses and treatment durations. However, the committee stated that these were all within an acceptable range for clinical practice and so all the results for fluconazole were grouped together for analysis. This decision was supported by analysis of model fit from the NMA, where the model fit for a model that combined all fluconazole doses was compared with models where the results were split by average and total dose of fluconazole (for more information see Appendix K and the methods document). Splitting the analysis by dose did not substantially improve model fit. With the exception of one study which used oral fluconazole, all other fluconazole doses were given intravenously while nystatin doses were given orally.

Fluconazole antifungal resistance outcomes from observational studies were at moderate or serious risk of bias and the overall effect estimate was very-low quality. Information on resistance was only available in relation to the use of fluconazole. Three studies reported on antifungal resistance, two of which were over 10 years old. Resistance patterns have changed over the past 10 years and so the results of these studies were not considered relevant. The third study was more recent but had a very small sample size and so the committee could not draw any conclusions in relation to antifungal resistance.

1.1.10.3 Imprecision and clinical importance of effects

Data from the network meta-analyses showed that for invasive fungal infection, both nystatin and fluconazole were favoured over placebo. The confidence intervals did not cross the line of no effect and the committee were satisfied that this reflected a genuine effect in comparison to placebo that was large enough to be clinically meaningful. The evidence could not differentiate between the effectiveness of nystatin and fluconazole, indicating that neither of the antifungal treatments are more clinically effective than the other. Confidence intervals were wider for the comparison between miconazole and placebo, where there was less evidence available for comparisons. The effect estimate was also near to the line of no effect, and so the committee decided that miconazole was unlikely to provide any clear benefits over placebo in reducing the risk of a baby developing fungal infection. The evidence could also not differentiate between the effectiveness of miconazole and other antifungals, which was likely to because of the limited evidence available to inform these comparisons.

The network meta-analysis for mortality suggested that fluconazole may reduce the risk of neonatal death in comparison to placebo, while the reduction in mortality with miconazole and nystatin were smaller and the confidence intervals crossed the line of no effect. There was a similar degree of imprecision in the analysis for all three of the antifungals. However, the committee highlighted that these results reflect all-cause mortality, rather than mortality specifically related to fungal infection. Much of the mortality in all treatment arms would be due to causes other than invasive fungal infection, which may contribute to the large amount of imprecision associated with this outcome. Therefore, these results were thought to have less clinical importance than the results for invasive fungal infection.

Length of stay network meta-analysis results indicated that none of the antifungals reduced hospital length of stay in comparison to placebo. These results had wide confidence intervals, which may reflect the smaller evidence base in comparison to the infection and mortality outcomes. Additional evidence is therefore needed to determine whether the use of antifungal prophylaxis can reduce length of stay and so the committee did not use this outcome as a basis for their recommendations. However, a research recommendation was not made in relation to this point as evidence from the length of stay outcome was not crucial to support recommendations. The committee made strong recommendations based on the evidence that was available and thought that further evidence on length of stay would not change these recommendations, and so a research recommendation was not justified.

Antifungal resistance outcomes were assessed using pairwise meta-analysis. However, given that two of the studies were published over 10 years before this review, the committee decided that much of the evidence was not relevant. The other study that reported on resistance outcomes had a very small sample size and wide confidence intervals. The committee decided that there was too much uncertainty in this result and so the evidence was not used when making recommendations. However, a research recommendation was not made in relation to this point as the committee thought that evidence from other outcomes was sufficient to support strong recommendations.

Other outcomes, such as neurodevelopmental outcomes and adverse events, relied on evidence from a single study. There was therefore a high degree of uncertainty associated

with these outcomes. As a result, the committee decided that recommendations should be based on the outcomes from the NMA and economic analysis rather than individual study analysis.

1.1.10.4 Benefits and harms

Overall, the committee agreed that evidence from the network meta-analyses favoured giving antifungal prophylaxis to prevent invasive fungal infection for preterm babies and those with low birthweight. The review question was specifically related to antifungal prophylaxis for babies treated with antibiotics for suspected late-onset neonatal infection, while the available evidence was for preterm or low birthweight babies who were not necessarily receiving antibiotic treatment. However, the committee agreed that this evidence could be extrapolated to preterm and low birthweight babies who were receiving antibiotics. The committee did not feel it could extrapolate these results to babies with birthweights above 1500g, but they noted that most babies given antibiotics for suspected late-onset infection are preterm or low birthweight babies. In the committee's experience there are very few babies beyond 30 weeks gestational age who would develop an invasive fungal infection.

Evidence on antifungal resistance was limited to fluconazole. The studies identified were mostly old and the committee noted the increased concern about antifungal resistance that has arisen in the last 5 years, and this potential harm of antifungal prophylaxis was taken into account by the committee. The committee noted that resistance is a greater concern for fluconazole than nystatin – for example a report by the World Health Organisation highlighted resistance to azoles as of worldwide concern (WHO 2014). Other potential harms include side effects of antifungals. Evidence was not identified to quantify these, but the committee noted that, in its experience, more serious side effects are possible with fluconazole than nystatin. The summary of product characteristics for fluconazole notes that side effects can include prolonged QT intervals on the electrocardiogram and skin reactions. The committee noted that nystatin is not associated with common side effects and is generally well tolerated. Together with evidence from the economic model the committee agreed that the balance of benefits and harms favoured nystatin over fluconazole as a first choice for antifungal prophylaxis.

This recommendation may increase the number of babies who are given antifungal prophylaxis when being treated with antibiotics for late-onset neonatal infection. However, the committee noted that current practice varies, with many centres already giving antifungal prophylaxis to these babies. By giving a clear recommendation that nystatin should be used as a first choice when antifungal prophylaxis is given, the recommendation may reduce the prescribing of fluconazole, which is of greatest concern for the development of antifungal resistance. The recommendation indicates that fluconazole should only be given in circumstances where oral administration of nystatin is not possible.

1.1.10.4 Cost effectiveness and resource use

The committee reviewed economic evidence on the cost effectiveness of antifungal prophylaxis. As there were no published studies included in the economic review, the evidence came solely from the economic model developed for this guideline.

In advising on an appropriate structure for the model, the committee noted that the obvious benefit of antifungal prophylaxis is reducing the incidence of fungal infection and its sequelae. The disadvantages that must be weighed against this benefit are the costs of antifungal agents, any short-term adverse events with which they are associated, and the risk of cultivating resistance in fungal pathogens. It was straightforward for the model to account for the costs of the agents; however, the other potential downsides of prophylaxis could not be quantified. Although, as noted above, fluconazole may have rare adverse

events, there was no evidence with which to estimate the incidence of these. The committee agreed that nystatin is associated with negligible toxicity. The impact of microbial resistance is also not practicably quantifiable without extensive, population-level mathematical modelling, especially as the clinical review found very little evidence about how the use of antifungals in the population of interest might influence it. However, the committee took this factor into account qualitatively when discussing the evidence. Therefore, the model represents a simple evaluation of the benefits of antifungal prophylaxis set against its immediate costs.

The committee agreed that degree of prematurity is a critical determinant of underlying risk of fungal infection (which will, in turn, define the value that prophylaxis might provide). Therefore, the model uses gestational age as an input that can be varied. Additionally, exposure to broad-spectrum antibiotics is known to be an important risk factor for invasive candidiasis. This is especially relevant for the present review question, for which the population comprises infants receiving antibiotics for suspected bacterial infections (for which, in some cases, broad-spectrum agents will be needed, as recommended in evidence review H - antibiotics). Therefore, the model was also configured to simulate populations with and without this exposure, to explore its influence on cost-effectiveness results.

The committee saw model results for cohorts with gestational ages from 22 to 42 weeks, with and without exposure to broad-spectrum antibiotics (amounting to 42 discrete scenarios). For gestational ages 22–33 weeks with or without exposure to broad-spectrum antibiotics, nystatin dominates both no prophylaxis and fluconazole, meaning nystatin is both less costly and results in more QALYs. For gestational ages 35–42 weeks with or without exposure to broad-spectrum antibiotics, nystatin no longer dominates no prophylaxis and has an incremental cost effectiveness ratio (ICER) worse than £20,000 per QALY. Fluconazole remains dominated by nystatin.

It is only for neonates born at 34 weeks' gestation that model results are quantitatively influenced by exposure to broad-spectrum antibiotics. Where broad-spectrum antibiotics are used, nystatin remains the dominant strategy; where there is no such exposure, neither nystatin nor fluconazole are good value for money (that is, they are both associated with ICERs worse than £20,000 per QALY).

The committee reviewed deterministic sensitivity analyses in which each of the model's input parameters in turn is varied within the range of its uncertainty. It saw that nystatin remains the optimal option compared with no prophylaxis in every instance in the most premature babies (gestational age less than 33 weeks, regardless of exposure to broad-spectrum antibiotics). As gestational age increases, the number of parameters by which nystatin remains the optimal option decreases until, at 37 weeks (38 weeks if broad-spectrum antibiotics are used), there is no model input parameter that can be varied within the range of its uncertainty such that nystatin is optimal.

The committee also saw deterministic sensitivity analyses illustrating the influence of individual model parameters on the comparison between nystatin and fluconazole. At lower gestational ages (<34 weeks), nystatin remains preferable when all except 2 of the inputs are varied within the range of their uncertainty. The odds ratios of infection for fluconazole versus placebo and for nystatin versus placebo are the sole parameters that can be changed such that fluconazole is favoured. This shows that the results of the head-to-head comparison are almost entirely determined by which strategy is more successful in avoiding cases of candidiasis.

The committee also reviewed a series of probabilistic sensitivity analyses. These show that:

- Nystatin has a high probability of being the optimal strategy at gestational ages of 22–28 weeks, with that approach providing the best balance of costs and benefits in around 80% of model iterations, regardless of exposure to broad-spectrum antibiotics.

Fluconazole is favoured in the remaining 20%; there are no model iterations in which no prophylaxis is preferred. This is consistent with the results of the NMA, where nystatin had approximately an 80% chance of being the best treatment in preventing cases of invasive fungal infections and placebo has no chance of being best; see rank probability histograms in appendix G.

- For gestational ages between 29–32 weeks, nystatin has an increased likelihood of providing the best balance of costs and benefits, exceeding 95% at 31 weeks (32 weeks with broad-spectrum antibiotics). At these gestational ages, there is very little probability that fluconazole is optimal; this is because the incremental benefits associated with prophylaxis are smaller, meaning the slightly higher costs of treatment with fluconazole are important even when the model samples values suggesting it may be associated with fewer cases of candidiasis than nystatin.
- From a gestational age of 32 weeks (33 weeks with exposure to broad-spectrum antibiotics), the probability that no prophylaxis provides the best balance of costs and benefits begins to rise. Beyond 34 weeks (35 weeks if broad-spectrum antibiotics are used), no prophylaxis is associated with the highest probability of being the best approach. Above 37 weeks (38 weeks with broad-spectrum antibiotics), the probability no prophylaxis is optimal exceeds 95%.

Based on these results, the committee felt confident recommending nystatin for antifungal prophylaxis, and fluconazole in cases where administration cannot be given orally. As already noted, the committee had increased confidence in this recommendation given nystatin not only is associated with fewer side effects, but it is also at a lower concern for antifungal resistance.

The committee discussed what criteria should be used to determine when a baby should be offered antifungal prophylaxis. Though the model indicates that nystatin should be given to any baby of gestational age lower than 34 weeks (or 35 weeks if broad-spectrum antibiotics are used), the results in later preterm babies arise because the model predicts it is worth offering a large number of neonates prophylaxis to prevent a single infection. This calculation only trades off the benefits of preventing infections against the costs of prophylaxis. The committee was mindful that the model does not account for other potential harms of prophylaxis, including the potential for antifungal resistance. Had antifungal resistance been incorporated into the model, it is likely the incremental net health benefits at all gestational ages would decrease. As such, the committee favoured a more conservative recommendation than the model suggested. The committee also considered whether it should tailor its recommendations to account for the additional risk presented by broad-spectrum antibiotics, but noted that this factor had a relatively small influence on model results. Although exposure to these agents results in a fairly large relative increase in the risk of invasive candidiasis (approximately doubling the odds of infection), the absolute risks involved become very small as gestational age rises. The committee noted that the model gives strong support for the use of antifungals in babies with gestation ages less than 30 weeks even where no such exposure is present.

In view of these considerations, the committee was confident in recommending prophylactic nystatin for babies treated with any type of antibiotics for suspected late-onset neonatal bacterial infection who have a birthweight of up to 1,500 g or are born at less than 30 weeks' gestation, and if oral administration is not possible, giving intravenous fluconazole.

The committee considered the potential resource impact of its recommendation. Committee members noted that a good proportion of units already give antifungal prophylaxis to all very low-birthweight babies (whether or not they are being treated for suspected bacterial infection), which substantially overlaps with the population, here. In cases where prophylaxis would be extended, the committee agreed the evidence shows that the relatively small costs

associated with antifungal agents are easily offset by greater savings in treating cases of candidiasis.

1.1.10.5 Other factors the committee took into account

The committee discussed whether the recommendation should include information on duration of antifungal prophylaxis. Most of the evidence gave antifungals to babies for a period of between 4 and 6 weeks. However, this evidence was in the indirect population of preterm and low birthweight babies rather than those being given antibiotics for suspected late-onset infection. The committee decided that it would be inappropriate to recommend this duration of prophylaxis for all babies who are being given antibiotics for suspected infection, as the most appropriate duration will vary depending on other circumstances, such as length of antibiotic treatment. In particular, a recommendation for 4-6 weeks of antifungal prophylaxis would not be appropriate if a baby who is given antibiotics for suspected infection then has a negative blood culture result and antibiotic treatment is stopped. A recommendation which results in a baby being given antifungals for longer than necessary could have adverse consequences for the baby as well as potentially increasing antifungal resistance. Instead, it was decided that neonatal units are likely to have their own prescribing policies which clinicians should continue to follow.

Although nystatin was the most clinically and cost-effective of the antifungals, the committee highlighted that there may be instances where a baby cannot be given oral antifungal prophylaxis, such as when they are very preterm. It was therefore decided that a recommendation for oral nystatin would not be appropriate in these circumstances. Consequently, additional guidance was added which recommends the use of intravenous fluconazole when it is not possible to prescribe oral nystatin.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendations 1.14.1 – 1.14.2.

1.1.12 References – included studies

1.1.12.1 Effectiveness

Systematic reviews

Austin, Nicola, Cleminson, Jemma, Darlow, Brian A et al. (2015) Prophylactic oral/topical non-absorbed antifungal agents to prevent invasive fungal infection in very low birth weight infants. The Cochrane database of systematic reviews: cd003478

Cleminson, Jemma; Austin, Nicola; McGuire, William (2015) Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants. The Cochrane database of systematic reviews: cd003850

Randomised controlled trials

Aydemir, Cumhur, Oguz, Serife Suna, Dizdar, Evrim Alyamac et al. (2011) Randomised controlled trial of prophylactic fluconazole versus nystatin for the prevention of fungal colonisation and invasive fungal infection in very low birth weight infants. Archives of disease in childhood. Fetal and neonatal edition 96(3): f164-8

Benjamin, Daniel K Jr, Hudak, Mark L, Duara, Shahnaz et al. (2014) Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: a randomized clinical trial. JAMA 311(17): 1742-9

Jannatdoust, A. and Imani, V. (2015) The effect of prophylactic intravenous fluconazole on the clinical outcome of preterm infants during hospitalization. International Journal of Women's Health and Reproduction Sciences 3(4): 212-216

Kaufman, D, Boyle, R, Hazen, K C et al. (2001) Fluconazole prophylaxis against fungal colonization and infection in preterm infants. The New England journal of medicine 345(23): 1660-6

Kaufman, David, Boyle, Robert, Hazen, Kevin C et al. (2005) Twice weekly fluconazole prophylaxis for prevention of invasive Candida infection in high-risk infants of <1000 grams birth weight. The Journal of pediatrics 147(2): 172-9

Kicklighter, S D, Springer, S C, Cox, T et al. (2001) Fluconazole for prophylaxis against candidal rectal colonization in the very low birth weight infant. Pediatrics 107(2): 293-8

Kirpal, Harita, Gathwala, Geeta, Chaudhary, Uma et al. (2016) Prophylactic fluconazole in very low birth weight infants admitted to neonatal intensive care unit: randomized controlled trial. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 29(4): 624-8

Manzoni, Paolo, Stolfi, Ilaria, Pugni, Lorenza et al. (2007) A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. The New England journal of medicine 356(24): 2483-95

Mersal, Ali, Alzahrani, Ibrahim, Azzouz, Mahasen et al. (2013) Oral Nystatin Versus Intravenous Fluconazole as Neonatal Antifungal Prophylaxis: Non-inferiority Trial. Journal of clinical neonatology 2(2): 88-92

Ozturk, Mehmet Adnan, Gunes, Tamer, Koklu, Esad et al. (2006) Oral nystatin prophylaxis to prevent invasive candidiasis in Neonatal Intensive Care Unit. Mycoses 49(6): 484-92

Parikh, Tushar B, Nanavati, Ruchi N, Patankar, Chandrakant V et al. (2007) Fluconazole prophylaxis against fungal colonization and invasive fungal infection in very low birth weight infants. Indian pediatrics 44(11): 830-7

Rundjan, L.; Wahyuningsih, R.; Oeswadi, C.A.; Marsogi, M.; Purnamasari, A.; Oral nystatin prophylaxis to prevent systemic fungal infection in very low birth weight preterm infants: A randomized controlled trial; BMC Pediatrics; 2020; vol. 20 (no. 1); 170

Sims M.E., Yoo Y, You H, Salminen C, Walther F.J. (1988) Prophylactic oral nystatin and fungal infections in very-low-birthweight infants. American Journal of Perinatology 5(1): 33-6Violaris, Kimon, Carbone, Tracy, Bateman, David et al. (2010) Comparison of fluconazole and nystatin oral suspensions for prophylaxis of systemic fungal infection in very low birthweight infants. American journal of perinatology 27(1): 73-8

Wainer S, Cooper P.A, Funk E, Bental R Y, Sandler D. A, Patel J. (1992) Prophylactic miconazole oral gel for the prevention of neonatal fungal rectal colonization and systemic infection. Pediatric Infectious Disease Journal 11(9):713-6

Observational studies

Lee, Juyoung, Kim, Han-Suk, Shin, Seung Han et al. (2016) Efficacy and safety of fluconazole prophylaxis in extremely low birth weight infants: multicenter pre-post cohort study. BMC pediatrics 16: 67

Manzoni, Paolo, Arisio, Riccardo, Mostert, Michael et al. (2006) Prophylactic fluconazole is effective in preventing fungal colonization and fungal systemic infections in preterm neonates: a single-center, 6-year, retrospective cohort study. Pediatrics 117(1): e22-32

Manzoni, P., Leonessa, M., Galletto, P. et al. (2008) Routine use of fluconazole prophylaxis in a neonatal intensive care unit does not select natively fluconazole-resistant candida subspecies. Pediatric Infectious Disease Journal 27(8): 731-737

Other references

WHO Antimicrobial Resistance: Global Report on Surveillance. 2014. [Accessed November 24, 2020]. Available from: http://www.who.int/drugresistance/documents/surveillancereport/en/

Appendices

Appendix A – Review protocols

Review protocol for what is the clinical and cost effectiveness of starting prophylactic antifungal treatment when starting antibiotic treatment for suspected late-onset neonatal infection?

ID	Field	Content
0.	PROSPERO registration number	CRD42020169891
1.	Review title	Prophylactic antifungals and antibiotics for treating late-onset neonatal infection
2.	Review question	What is the clinical and cost effectiveness of starting prophylactic antifungal treatment when starting antibiotic treatment for suspected late-onset neonatal infection?
3.	Objective	To establish the effectiveness of antifungal treatment in babies starting antibiotic treatment for suspected neonatal infection. To identify an effective and safe choice for antifungal prophylaxis (including the duration of antifungal treatment) when starting antibiotic treatment for suspected late-onset neonatal infection
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 • Conference abstracts 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 newborn babies. Late-onset neonatal infection occurs more than 72 hours after birth and can lead to life-threatening sepsis. Prompt antibiotic treatment for neonatal infection can save lives. Prophylactic antifungal treatment can also be started alongside antibiotic treatment for suspected late-onset neonatal infection to prevent fungal infection in newborns.
6.	Population	Inclusion: • Babies receiving antibiotic treatment for suspected late-onset neonatal bacterial infection

		Studies which report results for a mixed population of neonates with early-onset and late-onset neonatal infection will be included but evidence will be graded as indirectly applicable and sensitivity analyses will be conducted. Exclusion: • Babies with suspected or confirmed non-bacterial infections. • Babies with suspected or confirmed syphilis. • Babies with localised infections. • Babies with suspected or confirmed bacterial infection resulting from therapeutic interventions such as surgery. Babies with a history of surgery which was not the cause of the infection will not be excluded.
7.	Intervention/Exposure/Test	Antifungal prophylaxis treatments used alongside antibiotic treatment for neonatal infection, such as: • amphotericin B deoxycholate • fluconazole • micafungin • nystatin Antifungals will not be grouped by class for the purpose of the analysis.
8.	Comparator/Reference standard/Confounding factors	• Head-to-head comparison of any of the interventions listed above, including comparison of different treatment durations and doses • Placebo • No treatment

		• Usual care
9.	Types of study to be included	• Randomised controlled trials (RCTs) • Systematic reviews of RCTs • Observational studies (for antibiotic resistance outcome only, if insufficient RCT evidence is available for this outcome such that, in the committee's view, observational evidence could reasonably be expected to provide more robust information to inform decision making).
10.	Other exclusion criteria	• Non-English language studies • Conference abstracts, theses, dissertations
11.	Context	Most babies are treated on neonatal units or neonatal intensive care units. Babies admitted from home are usually treated on paediatric units or paediatric intensive care units.
12.	Primary outcomes (critical outcomes)	• Culture-proven invasive fungal 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 • Mortality (during the neonatal period at the latest time point reported in the study) • Length of hospital stay • Adverse drug reactions specifically related to antifungals) • Neurodevelopmental outcomes (measured using a validated tool at the latest time point reported in the study)

		• Antifungal resistance (culture proven) Family outcomes • psychological distress in baby's family as measured using a validated scale (e.g. parental stressor scale NICU; modified Rutter Malaise Inventory) (during the neonatal period and at the latest timepoint reported in study)
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. A stopping rule will be used to terminate screening if the following criteria are met:

		- At least 50% of the database has been screened - 500 records have been screened with no further included studies Reference lists of systematic reviews will also be checked for potential includes
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	• Antifungals will not be grouped by class for the purpose of the analysis.

		Subgroups (to be investigated irrespective of the presence of statistical heterogeneity) • term babies and preterm babies • current presence of central catheter • babies with history of previous surgery (in particular abdominal or cardiac surgery, surgery type will be noted by the reviewer and the committee consulted to determine if further subgrouping is appropriate)
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	01/01/2020
22.	Anticipated completion date	12/08/2020

23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	x	x
		Piloting of the study selection process	x	☐
		Formal screening of search results against eligibility criteria	x☐	☐
		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	Late onset neonatal infection, antifungal prophylaxis
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

Appendix B – Literature search strategies

Clinical search literature search strategy

The search was conducted on 20th March 2020. 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 (bacter?emia* or bacill?emia*).tw.

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

18 or/11-17

19 exp Streptococcus/

20 exp Staphylococcus/

21 (streptococc* or staphylococc*).tw.

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

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

24 exp Escherichia coli/

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

26 exp Listeria/

27 listeria*.tw.

28 exp Klebsiella/

29 klebsiella*.tw.

30 exp Pseudomonas/

31 (pseudomonas or chryseomonas or flavimonas).tw.

32 Enterobacteriaceae/

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

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

35 exp Neisseria/

36 neisseria*.tw.

37 exp Haemophilus influenzae/

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

39 exp Serratia/

40 serratia*.tw.

41 exp Cronobacter/

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

43 exp Acinetobacter/

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

45 exp Fusobacterium/

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

47 exp Enterococcus/

48 enterococc*.tw.

49 or/19-48

50 18 or 49

51 10 and 50

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

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

54 52 or 53

55 51 or 54

56 exp Mycoses/

57 (mycoses* or mycosis*).tw.

58 ((fung* or mycot* or yeast* or cryptococc*) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw.

59 (candidias* or candidemia* or fungemia*).tw.

60 (zygomycos* or phycomycos* or entomophthoramycos* or mucormycos* or mucoromycos*).tw.

61 ((cunninghamella* or absidia* or mortierella* or mucor* or rhizopus*) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw.

62 (aspergillos* or neuroaspergillos*).tw.

63 exp Candida/

64 (candida* or monilia* or torulops* or parapsilos* or orthopsilos* or metapsilos*).tw.

65 exp Saccharomyces/

66 saccharomyce*.tw.

67 Ascomycota/

68 (ascomyc* or cochliobol* or sclerotinia*).tw.

69 exp Aspergillus/

70 aspergillus*.tw.

71 or/56-70

72 10 and 71

73 55 or 72

74 exp Antifungal Agents/

75 (antifung* or anti-fung* or fungicid* or antimycot* or anti-mycot* or mycostat* or fung?stat*).tw.

76 Fluconazole/

77 (fluconazole* or azocan* or diflucan* or canesten*).tw.

78 Amphotericin B/

79 (amphotericin B or abelcet* or ambisome* or amphochild* or fungilin or fungizone* or amphotec* or amphocil*).tw.

80 Clotrimazole/

81 (clotrimazole* or abtrim* or fungederm* or masnoderm* or candiden* or mycil gold* or privacom* or lotriderm* or lotrimin* or femcare* or mycelex* or fungoid* or lotrisone*).tw.

82 Cycloheximide/

83 (c?cloheximide* or actidione*).tw.

84 Cyclosporine/

85 (cyclosporin* or capimune* or capsorin* or deximune* or ikervis* or neoral* or sandimmun* or sangcya* or cequa* or gengraf* or restasis* or vanquoral* or ciclosprin* or neoral*).tw.

86 exp Echinocandins/

87 (echinocandin* or mulundocandin* or aculeacin* or pneumocandin*).tw.

88 (anidulafungin* or ecalta* or eraxis*).tw.

89 (caspofungin* or cancidas*).tw.

90 (micafungin* or mycamine*).tw.

91 Flucytosine/

92 (flucytosine* or ancotil* or ancobon*).tw.

93 Griseofulvin/

94 (griseofulvin* or fulcin* or fulsovin* or grisol* or grisovin* or fulvicin* or grifulvin* or Gris-PEG* or grisactin*).tw.

95 Itraconazole/

96 (itraconazole* or sporanox* or onmel* or tolsura*).tw.

97 Ketoconazole/

98 (ketoconazole* or daktarin* or dandrazol* or dandrid* or nizoral* or extina* or ketodan* or xolegel*).tw.

99 Miconazole/

100 (miconazole* or dermonistat* or dumicoat* or femeron* or loramyc* or monistat* or acnidazil or acorvio* or daktacort* or aloe vesta* or azolen* or cruex* or desenex* or femizol-M* or fungoid* or Lotrimin AF* or M-Zole* or micatin* or miranel AF* or Neosporin AF* or oravig* or podactin* or vagistat* or ZeaSorb AF* or vusion*).tw.

101 Nystatin/

102 (nystatin* or infestat or nyspes* or nystamont* or nystan* or nystavescent* or dermovate* or flagyl compak* or gregoderm* or multilind* or mysteclin* or nystadermal* or nystaform* or timodine* or tinaderm* or trimovate* or tri-adcortyl* or tri-cicatrin* or mycostatin* or nilstat* or nystex* or Pedi-Dri or pediaderm* or myconel* or mytrex* or tri-statin* or nystop*).tw.

103 exp Sirolimus/

104 (sirolimus* or rapamune* or rapamycin* or everolimus* or afinitor* or certican* or votubia* or zortress*).tw.

105 Voriconazole/

106 (voriconazole* or vfend*).tw.

107 or/74-106

108 73 and 107

109 Animals/ not Humans/

110 108 not 109

111 limit 110 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 (bacter?emia* or bacill?emia*).tw.

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

18 or/11-17

19 exp Streptococcus/

20 exp Staphylococcus/

21 (streptococc* or staphylococc*).tw.

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

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

24 exp Escherichia coli/

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

26 exp Listeria/

27 listeria*.tw.

28 exp Klebsiella/

29 klebsiella*.tw.

30 exp Pseudomonas/

31 (pseudomonas or chryseomonas or flavimonas).tw.

32 Enterobacteriaceae/

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

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

35 exp Neisseria/

36 neisseria*.tw.

37 exp Haemophilus influenzae/

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

39 exp Serratia/

40 serratia*.tw.

41 exp cronobacter/

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

43 exp Acinetobacter/

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

45 exp Fusobacterium/

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

47 exp Enterococcus/

48 enterococc*.tw.

49 or/19-48

50 18 or 49

51 10 and 50

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

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

54 52 or 53

55 51 or 54

56 exp mycosis/

57 (mycoses* or mycosis*).tw.

58 ((fung* or mycot* or yeast* or cryptococc*) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw.

59 (candidias* or candidemia* or fungemia*).tw.

60 (zygomycos* or phycomycos* or entomophthoramycos* or mucormycos* or mucoromycos*).tw.

61 ((cunninghamella* or absidia* or mortierella* or mucor* or rhizopus*) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw.

62 (aspergillos* or neuroaspergillos*).tw.

63 exp Candida/

64 (candida* or monilia* or torulops* or parapsilos* or orthopsilos* or metapsilos*).tw.

65 exp Saccharomyces/

66 saccharomyce*.tw.

67 Ascomycetes/

68 (ascomyc* or cochliobol* or sclerotinia*).tw.

69 exp Aspergillus/

70 aspergillus*.tw.

71 or/56-70

72 10 and 71

73 55 or 72

74 exp antifungal agent/

75 (antifung* or anti-fung* or fungicid* or antimycot* or anti-mycot* or mycostat* or fung?stat*).tw.

76 fluconazole/

77 (fluconazole* or azocan* or diflucan* or canesten*).tw.

78 amphotericin B/

79 (amphotericin B or abelcet* or ambisome* or amphochild* or fungilin or fungizone* or amphotec* or amphocil*).tw.

80 clotrimazole/

81 (clotrimazole* or abtrim* or fungederm* or masnoderm* or candiden* or mycil gold* or privacom* or lotriderm* or lotrimin* or femcare* or mycelex* or fungoid* or lotrisone*).tw.

82 cycloheximide/

83 (c?cloheximide* or actidione*).tw.

84 cyclosporine/

85 (cyclosporin* or capimune* or capsorin* or deximune* or ikervis* or neoral* or sandimmun* or sangcya* or cequa* or gengraf* or restasis* or vanquoral* or ciclosprin* or neoral*).tw.

86 exp echinocandin/

87 (echinocandin* or mulundocandin* or aculeacin* or pneumocandin*).tw.

88 (anidulafungin* or ecalta* or eraxis*).tw. (

89 (caspofungin* or cancidas*).tw.

90 (micafungin* or mycamine*).tw.

91 flucytosine/

92 (flucytosine* or ancotil* or ancobon*).tw.

93 griseofulvin/

94 (griseofulvin* or fulcin* or fulsovin* or grisol* or grisovin* or fulvicin* or grifulvin* or Gris-PEG* or grisactin*).tw.

95 itraconazole/

96 (itraconazole* or sporanox* or onmel* or tolsura*).tw.

97 ketoconazole/

98 (ketoconazole* or daktarin* or dandrazol* or dandrid* or nizoral* or extina* or ketodan* or xolegel*).tw.

99 miconazole/

100 (miconazole* or dermonistat* or dumicoat* or femeron* or loramyc* or monistat* or acnidazil or acorvio* or daktacort* or aloe vesta* or azolen* or cruex* or desenex* or femizol-M* or fungoid* or Lotrimin AF* or M-Zole* or micatin* or miranel AF* or Neosporin AF* or oravig* or podactin* or vagistat* or ZeaSorb AF* or vusion*).tw.

101 nystatin/

102 (nystatin* or infestat or nyspes* or nystamont* or nystan* or nystavescent* or dermovate* or flagyl compak* or gregoderm* or multilind* or mysteclin* or nystadermal* or nystaform* or timodine* or tinaderm* or trimovate* or tri-adcortyl* or tri-cicatrin* or mycostatin* or nilstat* or nystex* or Pedi-Dri or pediaderm* or myconel* or mytrex* or tri-statin* or nystop*).tw.

103 rapamycin/

104 (sirolimus* or rapamune* or rapamycin* or everolimus* or afinitor* or certican* or votubia* or zortress*).tw.

105 voriconazole/

106 (voriconazole* or vfend*).tw.

107 or/74-106

108 73 and 107

109 nonhuman/ not human/

110 108 not 109

111 limit 110 to english language

112 limit 111 to (conference abstract or conference paper or "conference review")

113 111 not 112

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 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] 1 tree(s) exploded

#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] 2 tree(s) exploded

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

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

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

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

#18 {or #11-#17}

#19 MeSH descriptor: [Streptococcus] explode all trees

#20 MeSH descriptor: [Staphylococcus] explode all trees

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

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

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

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

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

#26 MeSH descriptor: [Listeria] explode all trees

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

#28 MeSH descriptor: [Klebsiella] explode all trees

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

#30 MeSH descriptor: [Pseudomonas] explode all trees

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

#32 MeSH descriptor: [Enterobacteriaceae] explode all trees

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

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

#35 MeSH descriptor: [Neisseria] explode all trees

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

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

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

#39 MeSH descriptor: [Serratia] explode all trees

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

#41 MeSH descriptor: [Cronobacter] explode all trees

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

#43 MeSH descriptor: [Acinetobacter] explode all trees

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

#45 MeSH descriptor: [Fusobacterium] explode all trees

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

#47 MeSH descriptor: [Enterococcus] explode all trees

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

#49 {or #19-#48}

#50 #18 or #49

#51 #10 and #50

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

#53 ((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

#54 #52 or #53

#55 #51 or #54

#56 MeSH descriptor: [Mycoses] explode all trees

#57 (mycoses* or mycosis*):ti,ab,kw

#58 ((fung* or mycot* or yeast* or cryptococc*) near/4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)):ti,ab,kw

#59 (candidias* or candidemia* or fungemia*):ti,ab,kw

#60 (zygomycos* or phycomycos* or entomophthoramycos* or mucormycos* or mucoromycos*):ti,ab,kw

#61 ((cunninghamella* or absidia* or mortierella* or mucor* or rhizopus*) near/4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)):ti,ab,kw

#62 (aspergillos* or neuroaspergillos):ti,ab,kw

#63 MeSH descriptor: [Candida] explode all trees

#64 (candida* or monilia* or torulops* or parapsilos* or orthopsilos* or metapsilos*):ti,ab,kw

#65 MeSH descriptor: [Saccharomyces] explode all trees

#66 (saccharomyce*):ti,ab,kw

#67 MeSH descriptor: [Ascomycota] this term only

#68 (ascomyc* or cochliobol* or sclerotinia*):ti,ab,kw

#69 MeSH descriptor: [Aspergillus] explode all trees

#70 (aspergillus):ti,ab,kw

#71 {or #56-#70}

#72 #10 and #71

#73 #55 or #72

#74 MeSH descriptor: [Antifungal Agents] explode all trees

#75 (antifung* or anti-fung* or fungicid* or antimycot* or anti-mycot* or mycostat* or fung?stat*):ti,ab,kw

#76 MeSH descriptor: [Fluconazole] this term only

#77 (fluconazole* or azocan* or diflucan* or canesten*):ti,ab,kw

#78 MeSH descriptor: [Amphotericin B] this term only

#79 (amphotericin B or abelcet* or ambisome* or amphochild* or fungilin or fungizone* or amphotec* or amphocil*):ti,ab,kw

#80 MeSH descriptor: [Clotrimazole] this term only

#81 (clotrimazole* or abtrim* or fungederm* or masnoderm* or candiden* or mycil gold* or privacom* or lotriderm* or lotrimin* or femcare* or mycelex* or fungoid* or lotrisone*):ti,ab,kw

#82 MeSH descriptor: [Cycloheximide] this term only

#83 (c?cloheximide* or actidione*):ti,ab,kw

#84 MeSH descriptor: [Cyclosporine] this term only

#85 (cyclosporin* or capimune* or capsorin* or deximune* or ikervis* or neoral* or sandimmun* or sangcya* or cequa* or gengraf* or restasis* or vanquoral* or ciclosprin* or neoral*):ti,ab,kw

#86 MeSH descriptor: [Echinocandins] explode all trees

#87 (echinocandin* or mulundocandin* or aculeacin* or pneumocandin*):ti,ab,kw

#88 (anidulafungin* or ecalta* or eraxis*):ti,ab,kw

#89 (caspofungin* or cancidas*):ti,ab,kw

#90 (micafungin* or mycamine*):ti,ab,kw

#91 MeSH descriptor: [Flucytosine] this term only

#92 (flucytosine* or ancotil* or ancobon*):ti,ab,kw

#93 MeSH descriptor: [Griseofulvin] this term only

#94 (griseofulvin* or fulcin* or fulsovin* or grisol* or grisovin* or fulvicin* or grifulvin* or Gris-PEG* or grisactin*):ti,ab,kw

#95 MeSH descriptor: [Itraconazole] this term only

#96 (itraconazole* or sporanox* or onmel* or tolsura*):ti,ab,kw

#97 MeSH descriptor: [Ketoconazole] this term only

#98 (ketoconazole* or daktarin* or dandrazol* or dandrid* or nizoral* or extina* or ketodan* or xolegel*):ti,ab,kw

#99 MeSH descriptor: [Miconazole] this term only

#100 (miconazole* or dermonistat* or dumicoat* or femeron* or loramyc* or monistat* or acnidazil or acorvio* or daktacort* or aloe vesta* or azolen* or cruex* or desenex* or femizol-

M* or fungoid* or Lotrimin AF* or M-Zole* or micatin* or miranel AF* or Neosporin AF* or oravig* or podactin* or vagistat* or ZeaSorb AF* or vusion*):ti,ab,kw

#101 MeSH descriptor: [Nystatin] this term only

#102 ((nystatin* or infestat or nyspes* or nystamont* or nystan* or nystavescent* or dermovate* or flagyl compak* or gregoderm* or multilind* or mysteclin* or nystadermal* or nystaform* or timodine* or tinaderm* or trimovate* or tri-adcortyl* or tri-cicatrin* or mycostatin* or nilstat* or nystex* or Pedi-Dri or pediaderm* or myconel* or mytrex* or tri-statin* or nystop*)):ti,ab,kw

#103 MeSH descriptor: [Sirolimus] explode all trees

#104 (sirolimus* or rapamune* or rapamycin* or everolimus* or afinitor* or certican* or votubia* or zortress*):ti,ab,kw

#105 MeSH descriptor: [Voriconazole] this term only

#106 (voriconazole* or vfend*):ti,ab,kw

#107 {or #74-#106}

#108 #73 and #107

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 (bacter?emia* or bacill?emia)

17 ((blood*) near4 (infect* or contamin* or invas* or invad*))

18 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

19 MeSH DESCRIPTOR Streptococcus EXPLODE ALL TREES

20 MeSH DESCRIPTOR Staphylococcus EXPLODE ALL TREES

21 (streptococc* or staphylococc*)

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

23 (met?icillin-resistant near3 aureus)

24 MeSH DESCRIPTOR escherichia coli EXPLODE ALL TREES

25 (((Escheric* or E) NEAR2 (coli) OR (ecoli*)))

26 MeSH DESCRIPTOR Listeria EXPLODE ALL TREES

27 (listeria*)

28 MeSH DESCRIPTOR Klebsiella EXPLODE ALL TREE

29 (Klebsiella*)

30 MeSH DESCRIPTOR Pseudomonas EXPLODE ALL TREES

31 (pseudomonas or chryseomonas or flavimonas)

32 MeSH DESCRIPTOR Enterobacteriaceae EXPLODE ALL TREES

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

34 ((enteric or coliform) near2 (bac*))

35 MeSH DESCRIPTOR Neisseria EXPLODE ALL TREES

36 (neisseria*)

37 MeSH DESCRIPTOR Haemophilus influenzae EXPLODE ALL TREES

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) near2 (influenz* or pfeiffer* or meningitidis))

39 MeSH DESCRIPTOR Serratia EXPLODE ALL TREES

40 (serratia*)

41 MeSH DESCRIPTOR Cronobacter EXPLODE ALL TREES

42 (cronobact* or sakazaki* or malonatic*)

43 MeSH DESCRIPTOR Acinetobacter EXPLODE ALL TREES

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

45 MeSH DESCRIPTOR Fusobacterium EXPLODE ALL TREES

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

47 MeSH DESCRIPTOR Enterococcus EXPLODE ALL TREES

48 (enterococc*)

49 #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 OR #47 OR #48

50 #18 OR #49

51 #10 AND #50

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) near4 (infect*))

53 ((premature* or pre-mature* or preterm* or pre-term*) near4 (child* or infant* or baby* or babies* or offspring) near4 (infect*))

54 #52 OR #53

55 #51 OR #54

56 MeSH DESCRIPTOR mycoses EXPLODE ALL TREES

57 (mycoses* or mycosis*)

58 ((fung* or mycot* or yeast* or cryptococc*) near4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)

59 (candidias* or candidemia* or fungemia*)

60 (zygomycos* or phycomycos* or entomophthoramycos* or mucormycos* or mucoromycos*)

61 ((cunninghamella* or absidia* or mortierella* or mucor* or rhizopus*) near4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*))

62 (aspergillos* or neuroaspergillos*)

63 MeSH DESCRIPTOR candida EXPLODE ALL TREES

64 (candida* or monilia* or torulops* or parapsilos* or orthopsilos* or metapsilos*)

65 MeSH DESCRIPTOR Saccharomyces EXPLODE ALL TREES

66 (saccharomyce*)

67 MeSH DESCRIPTOR Ascomycota

68 (ascomyc* or cochliobol* or sclerotinia*)

69 MeSH DESCRIPTOR Aspergillus EXPLODE ALL TREES

70 (aspergillus*)

71 #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70

72 #10 AND #71

73 #55 OR #72

74 MeSH DESCRIPTOR Antifungal Agents EXPLODE ALL TREES

75 (antifung* or anti-fung* or fungicid* or antimycot* or anti-mycot* or mycostat* or fung?stat*)

76 MeSH DESCRIPTOR Fluconazole

77 (fluconazole* or azocan* or diflucan* or canesten*)

78 MeSH DESCRIPTOR Amphotericin B

79 (amphotericin B or abelcet* or ambisome* or amphochild* or fungilin or fungizone* or amphotec* or amphocil*)

80 MeSH DESCRIPTOR Clotrimazole

81 (clotrimazole* or abtrim* or fungederm* or masnoderm* or candiden* or mycil gold* or privacom* or lotriderm* or lotrimin* or femcare* or mycelex* or fungoid* or lotrisone*)

82 MeSH DESCRIPTOR Cycloheximide

83 (c?cloheximide* or actidione*)

84 MeSH DESCRIPTOR Cyclosporine

85 (cyclosporin* or capimune* or capsorin* or deximune* or ikervis* or neoral* or sandimmun* or sangcya* or cequa* or gengraf* or restasis* or vanquoral* or ciclosprin* or neoral*)

86 MeSH DESCRIPTOR Echinocandins EXPLODE ALL TREES

87 (echinocandin* or mulundocandin* or aculeacin* or pneumocandin*)

88 (anidulafungin* or ecalta* or eraxis*)

89 (caspofungin* or cancidas*)

90 (micafungin* or mycamine*)

91 MeSH DESCRIPTOR Flucytosine

92 (flucytosine* or ancotil* or ancobon*)

93 MeSH DESCRIPTOR Griseofulvin

94 (griseofulvin* or fulcin* or fulsovin* or grisol* or grisovin* or fulvicin* or grifulvin* or Gris-PEG* or grisactin*)

95 MeSH DESCRIPTOR Itraconazole

96 (itraconazole* or sporanox* or onmel* or tolsura*)

97 MeSH DESCRIPTOR Ketoconazole

98 (ketoconazole* or daktarin* or dandrazol* or dandrid* or nizoral* or extina* or ketodan* or xolegel*)

99 MeSH DESCRIPTOR Miconazole

100 (miconazole* or dermonistat* or dumicoat* or femeron* or loramyc* or monistat* or acnidazil or acorvio* or daktacort* or aloe vesta* or azolen* or cruex* or desenex* or femizol-

M* or fungoid* or Lotrimin AF* or M-Zole* or micatin* or miranel AF* or Neosporin AF* or oravig* or podactin* or vagistat* or ZeaSorb AF* or vusion*)

101 MeSH DESCRIPTOR Nystatin

102 (nystatin* or infestat or nyspes* or nystamont* or nystan* or nystavescent* or dermovate* or flagyl compak* or gregoderm* or multilind* or mysteclin* or nystadermal* or nystaform* or timodine* or tinaderm* or trimovate* or tri-adcortyl* or tri-cicatrin* or mycostatin* or nilstat* or nystex* or Pedi-Dri or pediaderm* or myconel* or mytrex* or tri-statin* or nystop*)

103 MeSH DESCRIPTOR Sirolimus EXPLODE ALL TREES

104 (sirolimus* or rapamune* or rapamycin* or everolimus* or afinitor* or certican* or votubia* or zortress*)

105 MeSH DESCRIPTOR Voriconazole

106 (voriconazole* or vfend*)

107 #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106

108 #73 AND #107

109 * IN DARE

110 #108 AND #109

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

Observational Studies

1 Observational Studies as Topic/

2 Observational Study/

3 Epidemiologic Studies/

4 exp Case-Control Studies/

5 exp Cohort Studies/

6 Cross-Sectional Studies/

7 Controlled Before-After Studies/

8 Historically Controlled Study/

9 Interrupted Time Series Analysis/

10 Comparative Study.pt.

11 case control$.tw.

12 case series.tw.

13 (cohort adj (study or studies)).tw.

14 cohort analy$.tw.

15 (follow up adj (study or studies)).tw.

16 (observational adj (study or studies)).tw.

17 longitudinal.tw.

18 prospective.tw.

19 retrospective.tw.

20 cross sectional.tw.

21 or/1-20

Antibiotic resistance terms.

The following terms were used for all databases and combined as 'AND' with the observational studies filter.

1 Drug Resistance, Microbial/

2 exp Drug Resistance, Bacterial/

3 Drug Resistance, Multiple/

4 (AR or AMR or ABR or MDR or MBR).tw.

5 (resist* or tolera* or nonsuscept* or non-suscept*).tw.

6 R Factors/

7 (r adj2 (factor* or plasmid*)).tw.

8 Superinfection/

9 (superbug* or super bug* or superinfect* or super infect* or superinvas* or super invas*).tw.

10 ((inappropriat* or irrational* or imprudent* or unnecessar* or incorrect* or irrespons* or misus* or improper* or error* or mistake* or indiscriminat* or suboptim* or sub-optim* or bad or badly or inefficient* or uncontrol* or overus* or excess* or vary* or varia* or poor*) adj4 (antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid* or bacteriostat*) adj4 (prescr* or adminis* or dispens* or "use" or usag* or utili* or provi* or distribut* or therap* or treatment* or expos* or consum*)).tw.

11 or/1-10

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)

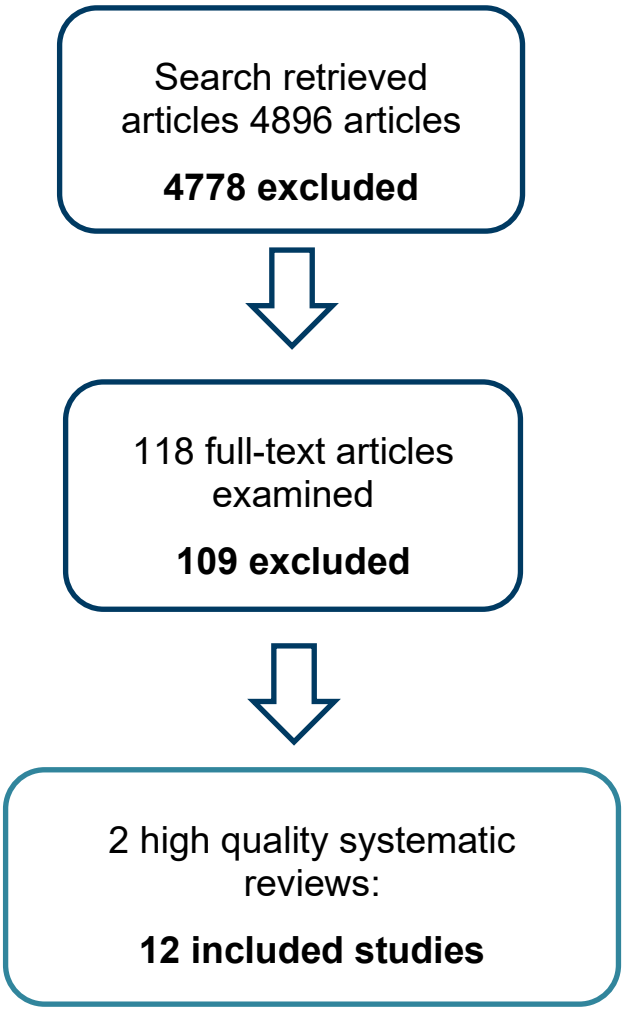
29 25 or 28 (205)

30 3 and 29 (15)

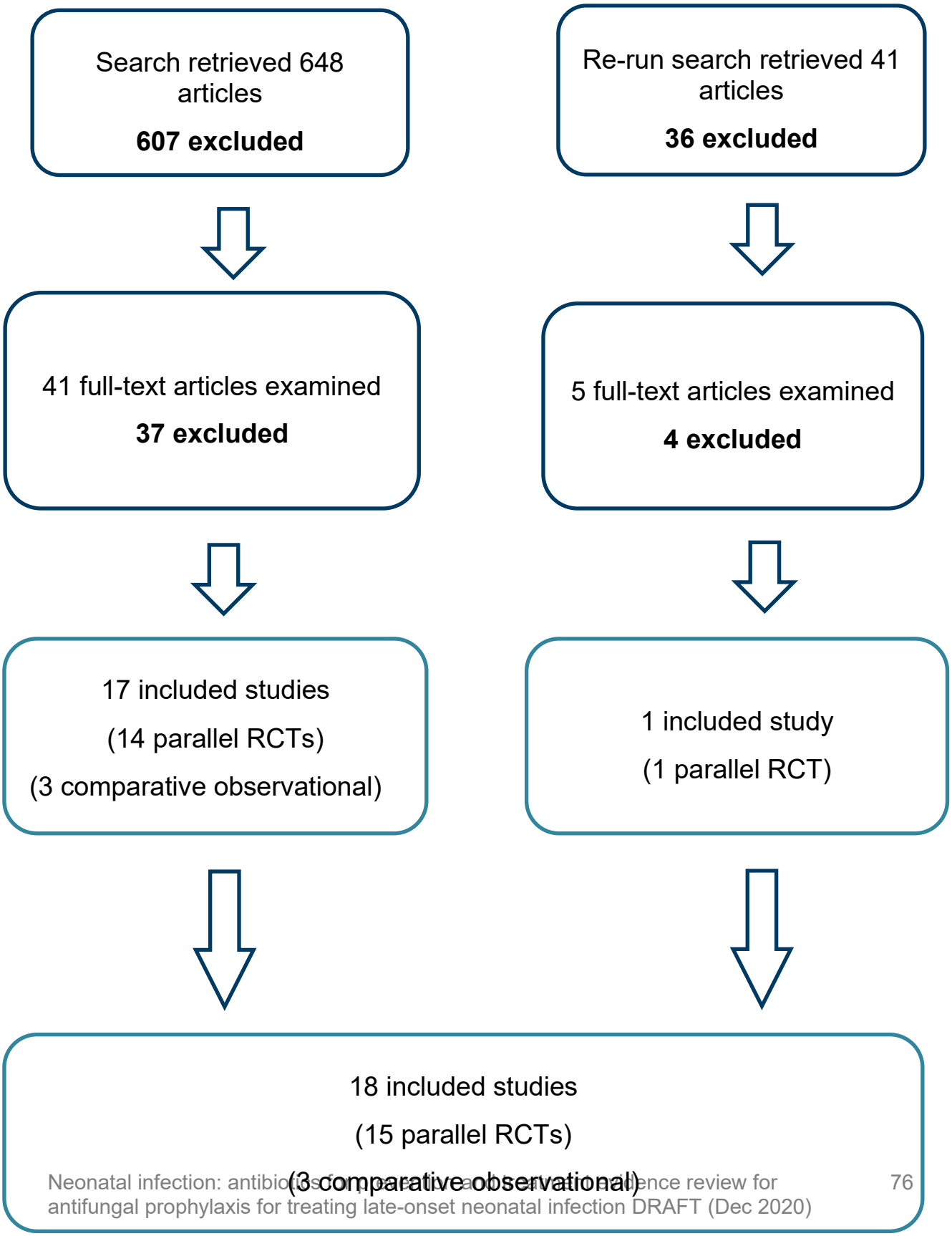
31 limit 30 to yr="2019 -Current" (1)

Appendix C – Effectiveness evidence study selection

Initial search



Follow-up search (preterm and low birthweight babies)



Appendix D – Effectiveness evidence

Systematic reviews

Austin, 2015

Bibliographic Reference	Austin, Nicola; Cleminson, Jemma; Darlow, Brian A; McGuire, William; Prophylactic oral/topical non-absorbed antifungal agents to prevent invasive fungal infection in very low birth weight infants.; The Cochrane database of systematic reviews; 2015; (no. 10); cd003478

Study Characteristics

Study design	Systematic review
Study details	Dates searched Up to May 2015 Databases searched Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, Sources of funding Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA UK National Institute of Health Research Grant (NIHR) Cochrane Programme Grant (13/89/12)
Inclusion criteria	Randomised or quasi-randomised controlled trials, including cluster randomised trials VLBW infants (less than 1500 grams) or very preterm infants (less than 32 weeks at birth) Antifungal prophylaxis with oral/topical non-absorbed drugs versus placebo or nothing or another antifungal drug regimen.
Exclusion criteria	None reported
Intervention(s)	Antifungal prophylaxis with oral/topical non-absorbed drugs Placebo/no treatment

Outcome(s)	Confirmed invasive fungal infection Determined by: a. culture of fungus from a normally sterile site: cerebrospinal fluid, blood, urine, bone or joint, peritoneum, pleural space. Samples should have been collected using methods to minimise contamination with surface-colonising organisms; b. findings on autopsy examination consistent with invasive fungal infection; c. findings on ophthalmological examination consistent with fungal ophthalmitis or retinitis; d. pathognomonic findings on renal ultrasound examination such as 'renal fungal balls'. Death prior to hospital discharge Neurodevelopmental outcomes assessed beyond infancy neurological evaluations, developmental scores, and classifications of disability, including auditory and visual disability, non-ambulant cerebral palsy, developmental delay); and cognitive and educational outcomes atfive years or older (intelligence quotient and/or indices of educational achievement measured using a validated tool including school examination results)
Number of studies included in the systematic review	7
Studies from the systematic review that are relevant for use in the current review	Sims 1988 Wainer 1992 Ozturk 2006 Violaris 2010 Aydemir 2011 Mersal 2013

Risk of bias

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
	Were the eligibility criteria appropriate for the review question?	Yes

Section	Question	Answer
	Were eligibility criteria unambiguous?	Yes
	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes
	Were methods additional to database searching used to identify relevant reports?	Yes
	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes
	Were restrictions based on date, publication format, or language appropriate?	Yes
	Were efforts made to minimise error in selection of studies?	Yes
	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Were efforts made to minimise error in data collection?	Yes

Section	Question	Answer
	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes
	Were all relevant study results collected for use in the synthesis?	Yes
	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
	Were efforts made to minimise error in risk of bias assessment?	Yes
	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Did the synthesis include all studies that it should?	Yes
	Were all pre-defined analyses reported or departures explained?	Yes
	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes
	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Yes
	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Yes
	Were biases in primary studies minimal or addressed in the synthesis?	Yes

Section	Question	Answer
	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low
	Applicability as a source of data	Partially applicable *(Indirectly applicable - Antifungal prophylaxis for preterm or VLBW babies, rather than prophylaxis for babies being given antibiotics for late-onset infection)*

Cleminson, 2015

Bibliographic Reference Cleminson, Jemma; Austin, Nicola; McGuire, William; Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants.; The Cochrane database of systematic reviews; 2015; (no. 10); cd003850

Study Characteristics

Study design	Systematic review
Study details	Dates searched Until May 2015 Databases searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL Sources of funding UK National Institute of Health Research Grant (NIHR) Cochrane Programme Grant (13/89/12)
Inclusion criteria	Randomised or quasi-randomised controlled trials, including cluster randomised trials Cluster randomised trials where the unit of randomisation was the neonatal nursery VLBW infants (less than 1500 grams) or very preterm infants (less than 32 weeks at birth) with or without evidence of fungal colonisation but without evidence of invasive fungal infection at study entry

Exclusion criteria	None reported
Intervention(s)	Placebo/no treatment Systemic antifungal prophylaxis Topical antifungal prophylaxis Oral antifungal prophylaxis
Outcome(s)	Confirmed invasive fungal infection Determined by • culture of fungus from a normally sterile site e.g. cerebrospinal fluid, blood, urine, bone or joint, peritoneum, pleural space; • findings on autopsy examination consistent with invasive fungal infection; • findings on ophthalmological examination consistent with fungal ophthalmitis or retinitis; • pathognomonic findings on renal ultrasound examination such as 'renal fungal balls'. Death prior to hospital discharge Neurodevelopmental outcomes assessed beyond infancy (i) neurodevelopmental outcomes assessed using validated tools at 12 months or more corrected age, and classifications of disability including non-ambulant cerebral palsy, developmental delay, auditory and visual impairment; (ii) cognitive and educational outcomes at 5 years or more e.g. intelligence quotient or indices of educational achievement measured using a validated tool (including school examination results). Bronchopulmonary dysplasia oxygen supplementation at 36 weeks postmenstrual age Necrotising enterocolitis Bell stage 2 or 3 Retinopathy of prematurity a) any stage; b) requiring treatment Duration of intensive care unit or hospital admission (days) Emergence of organisms resistant to antifungal agents as detected in individual infants enrolled in the study or, in the case of cluster randomised studies, on surveillance of other infants in the same unit in the study centre (including infants who were admitted to the unit following completion of the study) Adverse drug reactions attributed to the antifungal agent

Number of studies included in the systematic review	15
Studies from the systematic review that are relevant for use in the current review	Violaris 2010 Aydemir 2011 Mersal 2013 Kicklighter 2001 Cabrera 2002 Kaufman 2005 Manzoni 2007 Parikh 2007 Kirpal 2015 Benjamin 2014
Studies from the systematic review that are not relevant for use in the current review	Arrieta 2010, Kim 2010,

Risk of bias

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Yes

Section	Question	Answer
	Were the eligibility criteria appropriate for the review question?	Yes
	Were eligibility criteria unambiguous?	Yes
	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes
	Were methods additional to database searching used to identify relevant reports?	Yes
	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes
	Were restrictions based on date, publication format, or language appropriate?	Yes
	Were efforts made to minimise error in selection of studies?	Yes
	Concerns regarding methods used to identify and/or select studies	Low

Section	Question	Answer
Data collection and study appraisal	Were efforts made to minimise error in data collection?	Yes
	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes
	Were all relevant study results collected for use in the synthesis?	Yes
	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
	Were efforts made to minimise error in risk of bias assessment?	Yes
	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Did the synthesis include all studies that it should?	Yes
	Were all pre-defined analyses reported or departures explained?	Yes
	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes
	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Yes
	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Yes

Section	Question	Answer
	Were biases in primary studies minimal or addressed in the synthesis?	Yes
	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low
	Applicability as a source of data	Partially applicable *(Indirectly applicable - Antifungal prophylaxis for preterm or VLBW babies, rather than prophylaxis for babies being given antibiotics for late-onset infection)*

Randomised controlled trials

For evidence tables and risk of bias for other studies, see systematic reviews (Cleminson 2015 and Austin 2015)

Jannatdoust, 2015

Bibliographic Reference	Jannatdoust, A.; Imani, V.; The effect of prophylactic intravenous fluconazole on the clinical outcome of preterm infants during hospitalization; International Journal of Women's Health and Reproduction Sciences; 2015; vol. 3 (no. 4); 212-216

Study details

Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	NICU of Al-Zahra hospital and Pediatrics hospital

Study dates	Not reported
Duration of follow-up	During hospitalisation
Sources of funding	None
Inclusion criteria	Premature infants <32 weeks gestational age Birthweight <1250 g
Exclusion criteria	Major congenital abnormalities
Sample size	93
Interventions	Fluconazole v placebo
Outcome measures	Length of hospital stay Mortality

Study arms

Fluconazole (N = 43)

6-week treatment with 3 mg/kg dose of fluconazole every 3 days in the first 2 weeks, every 2 days in second 2 weeks and every day in the third 2 weeks

Split between study groups	43

Loss to follow-up	0
Condition specific characteristics	Gestational age (weeks) Mean (SD): 28.41 (1.57) Birth weight (g) Mean (SD): 968.8 (163.3)

No treatment (N = 50)

Condition specific characteristics	Gestational age (weeks) Mean (SD): 28.76 (2.1) Birth weight (g) Mean (SD): 976.3 (203.3)

Characteristics

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	No information *(States that trial was randomised but no further information)*
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Some concerns *(Limited information about randomisation and allocation concealment)*

Section	Question	Answer
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?	No information
	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 information
	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)	High *(No information about blinding and 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?	Probably no

Section	Question	Answer
	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 ?	No information
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low *(Unclear whether outcome assessors were aware of the intervention received but outcomes were objective)*
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?	No information
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	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	High *(Limited information about randomisation, blinding or analysis methods)*

Section	Question	Answer
	Overall Directness	Indirectly applicable *(Fluconazole for neonates, but includes babies in both the early- and late-onset periods and gives antifungals not necessarily alongside antibiotics)*

Rundjan, 2020

Bibliographic Reference Rundjan, L.; Wahyuningsih, R.; Oeswadi, C.A.; Marsogi, M.; Purnamasari, A.; Oral nystatin prophylaxis to prevent systemic fungal infection in very low birth weight preterm infants: A randomized controlled trial; BMC Pediatrics; 2020; vol. 20 (no. 1); 170

Study details

Study type	Randomised controlled trial (RCT)
Study location	Indonesia
Study setting	Neonatal intensive care unit of Cipto Mangunkusumo Hospital
Study dates	October 2010 - November 2012
Duration of follow-up	Duration of antifungal treatment
Sources of funding	None
Inclusion criteria	Inborn infants admitted to the neonatal intensive care unit within the first 72 h of life who had a gestational age of ≤ 32 weeks and/or birth weight of ≤ 1500 g.
Exclusion criteria	Infants <28 weeks gestational age or <1000 g

Sample size	95
Interventions	Nystatin Control (no treatment)
Outcome measures	Invasive fungal infection During duration of antifungal treatment Mortality During duration of antifungal treatment

Study arms

Nystatin (N = 47)

Oral nystatin (Mycostatin oral suspension 100.000 U/mL, manufactured by Taisho Pharmaceuticals Indonesia) with a dosage of 1 mL (0.5 mL was coated in oral cavity and another 0.5 mL was given through orogastric tube) three times a day for the six weeks of the study period or until no risk factors of SFI were noted.

Split between study groups	47
Condition specific characteristics	Mean gestational age (SD) 30.8 weeks (2.0) % female 48.9% Mean birth weight (SD) 1290 g (234.6)

Control (N = 48)

1 mL of sterile water three times a day as a coating in oral cavity as according to the hospital protocol of oral hygiene care

Split between study groups	48
Condition specific characteristics	Mean gestational age (SD) 30.5 weeks (2.2) % female 33.3% Mean birth weight (SD) 1318 g (259.2)

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?	No
	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
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
	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?	Yes
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
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?	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

Section	Question	Answer
	Risk-of-bias judgement for measurement of the outcome	Low *(Study was not blinded but outcomes were objective)*
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 (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	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	Low
	Overall Directness	Directly applicable

Observational studies

Lee, 2016

Bibliographic Reference Lee, Juyoung; Kim, Han-Suk; Shin, Seung Han; Choi, Chang Won; Kim, Ee-Kyung; Choi, Eun Hwa; Kim, Beyong Il; Choi, Jung-Hwan; Efficacy and safety of fluconazole prophylaxis in extremely low birth weight infants: multicenter pre-post cohort study.; BMC pediatrics; 2016; vol. 16; 67

Study details

Study type	Retrospective cohort study
Study location	Korea
Study setting	NICUs of Seoul National University Children's Hospital and Seoul National University Bundang Hospital
Study dates	March 2003 - February 2013
Duration of follow-up	During hospitalisation
Sources of funding	Ministry of Food and Drug Safety of Korea
Inclusion criteria	Extremely low birthweight
Exclusion criteria	Infants prenatally exposed to antifungal agents Receiving therapeutic antifungal agents within 3 days after birth Babies who died before 3 days of life
Sample size	423

Study arms

Pre-prophylaxis period (no treatment) (N = 159)

Split between study groups	159

Condition specific characteristics	Gestational age (weeks) Mean (SD): 27+1 (2+3) Birth weight (g) Mean (SD): 761 (153)

Prophlaxis period (Fluconazole) (N = 264)

3 mg/kg fluconazole administered once a day intravenously if a catheter was present, or through an orogastric tube, starting on the 3rd postnatal day,,twice a week for 4 weeks.

Split between study groups	264
Condition specific characteristics	Gestational age (weeks) Mean (SD): 27+0 (2+1) Birth weight (g) Mean (SD): 775 (154)

Characteristics

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Probably no
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable

Section	Question	Answer
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Not applicable
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
	Risk of bias judgement for confounding	Moderate *(Limited information about analysis methods)*
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
	2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes
	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
	Risk of bias judgement for classification of interventions	Low

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
	4.3. Were important co-interventions balanced across intervention groups?	Not applicable
	4.4. Was the intervention implemented successfully for most participants?	Yes
	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
	5.2 Were participants excluded due to missing data on intervention status?	No information
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
	Risk of bias judgement for missing data	Moderate *(Limited information provided)*
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably no
	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes

Section	Question	Answer
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate *(Limited information about analysis methods)*
	Directness	Indirectly Applicable *(Includes babies within the period for early-onset infection. Antifungals not necessarily given at the same time as antibiotics)*

Manzoni, 2008

Bibliographic Reference	Manzoni, P.; Leonessa, M.; Galletto, P.; Latino, M.A.; Arisio, R.; Maule, M.; Agriesti, G.; Gastaldo, L.; Gallo, E.; Mostert, M.; Farina, D.; Routine use of fluconazole prophylaxis in a neonatal intensive care unit does not select natively fluconazole-resistant candida subspecies; Pediatric Infectious Disease Journal; 2008; vol. 27 (no. 8); 731-737

Study details

Study type	Retrospective cohort study
Study location	Italy
Study setting	Level III unit at Turin hospital
Study dates	July 1997 - December 2006
Duration of follow-up	During hospital stay
Sources of funding	None reported
Inclusion criteria	Survived longer than 3 days
Exclusion criteria	Incomplete data Incomplete weekly surveillance cultures
Sample size	719
Interventions	Fluconazole v no treatment
Outcome measures	Antifungal resistance

Study arms

Pre-prophylaxis (no treatment) (N = 285)

Split between study groups	285
Loss to follow-up	0
% Female	Gender not reported for all patients
Condition specific characteristics	Gestational age (weeks) Mean (SD): 29.8 (3) Birth weight (g) Mean (SD): 1218 (275)

Post-prophylaxis (fluconazole) (N = 434)

6 mg/kg fluconazole every 72 hours in the first week of life, then every 48 hours from the second week until 30 days of life for neonates with birth weight 1000- 1500 g, 45 days of life for ELBW neonates, or until earlier discharge, or the need for systemic antifungal therapy due to the onset of invasive fungal infection. Schedule was partially modified during a 15-month period between 2004 and 2005, when approximately one third of the VLBW neonates received 3 mg/kg and another third did not receive fluconazole

Split between study groups	434
Loss to follow-up	0
% Female	52%
Condition specific characteristics	Gestational age (weeks) Mean (SD): 28.3 (3)

	Birth weight (g) Mean (SD): 28.3 (3)

Characteristics

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Probably no
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Not applicable
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
	Risk of bias judgement for confounding	Moderate *(Limited information about analysis methods)*

Section	Question	Answer
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
	2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes
	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Yes
	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Yes *(For 15-months between 2004 and 2005, approximately one third of the VLBW neonates (in the prophylaxis group) received 3 mg/kg instead of 6 mg/kg and*

Section	Question	Answer
		another third did not receive fluconazole. Changes to the regime were because of participation in a multicenter trial on fluconazole)
	4.3. Were important co-interventions balanced across intervention groups?	Not applicable
	4.4. Was the intervention implemented successfully for most participants?	No *(Over a 15 month period, two thirds of babies in the fluconazole group did not receive the correct intervention)*
	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
	Risk of bias judgement for deviations from intended interventions	Critical *(Over 15 months, two thirds of the babies in the fluconazole group did not receive the expected dose of fluconazole, or received no fluconazole)*
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
	5.2 Were participants excluded due to missing data on intervention status?	No information
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No
	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
	Risk of bias judgement for missing data	Low

Section	Question	Answer
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably no
	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably no
	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
	Risk of bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious *(Over a 15 month period, two-thirds of the babies in the fluconazole group received either a lower dose of fluconazole or no fluconazole. Limited information about analysis methods)*
	Directness	Indirectly Applicable *(Babies who may have had early-onset infection and not necessarily given antifungals alongside antibiotics)*

Manzoni, 2006

Bibliographic Reference Manzoni, Paolo; Arisio, Riccardo; Mostert, Michael; Leonessa, MariaLisa; Farina, Daniele; Latino, Maria Agnese; Gomirato, Giovanna; Prophylactic fluconazole is effective in preventing fungal colonization and fungal systemic infections in preterm neonates: a single-center, 6-year, retrospective cohort study.; Pediatrics; 2006; vol. 117 (no. 1); e22-32

Study details

Study type	Retrospective cohort study
Study location	Italy
Study setting	NICU
Study dates	January 1998 - December 2003
Duration of follow-up	30 days (45 days for extremely low birth weight infants)
Sources of funding	None reported

Inclusion criteria	Survived longer than 3 days
Exclusion criteria	Incomplete data Incorrect prophylaxis Abnormal serum liver enzyme levels on enrolment
Sample size	465
Interventions	Fluconazole v no treatment
Outcome measures	Antifungal resistance

Study arms

Pre-prophlaxis period (no treatment) (N = 240)

Neonates who were born in the period 1998–2000 when fluconazole prophylaxis was not used

Split between study groups	240
Loss to follow-up	0
Condition specific characteristics	Birth weight (g) Mean: 1212 g

Prophylaxis period (fluconazole) (N = 225)

Neonates who were born in the period 2001–2003, all of whom received prophylactic fluconazole. 6 mg/kg fluconazole every 72 hours in the first week of life, then every 48 hours from the second week. Given until 30 days for very low birth weight, 45 days for extremely low birth weight or until earlier discharge or until the need for systemic antifungal therapy as a result of the onset of proven or presumed SFI. Fluconazole was administered starting from dol 1 as a single dose intravenously or orally, depending on the availability of a venous line and/or on the tolerance of oral feeding.

Split between study groups	225
Loss to follow-up	0
Condition specific characteristics	Birth weight (g) Mean: 1108 g

Characteristics

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Probably yes *(Significant difference in mean birth weight of the babies in each trial arm)*
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably no
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Not applicable

Section	Question	Answer
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
	Risk of bias judgement for confounding	Serious *(Baseline differences - significant difference in birth weight between trial arms. Limited information about analysis methods)*
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
	2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes
	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
	Risk of bias judgement for classification of interventions	Low

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
	4.3. Were important co-interventions balanced across intervention groups?	Not applicable
	4.4. Was the intervention implemented successfully for most participants?	Yes
	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
	5.2 Were participants excluded due to missing data on intervention status?	Yes
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Yes
	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably no
	6.2 Were outcome assessors aware of the intervention received by study participants?	No information

Section	Question	Answer
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate *(Differences in baseline characteristics (birth weight). Limited information about analysis methods)*
	Directness	Indirectly Applicable *(Includes babies with early-onset infection. Antifungals not necessarily given alongside antibiotics)*

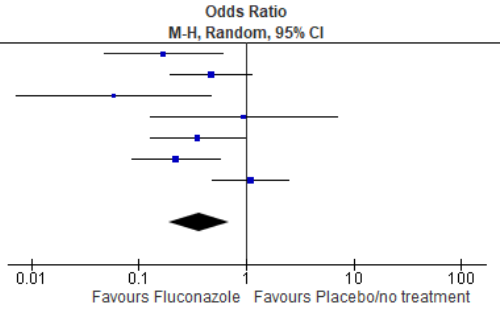
Appendix E – Forest plots

Fluconazole v placebo / no treatment

Invasive fungal infection

Study or Subgroup	Fluconazole Events	Fluconazole Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Odds Ratio M-H, Random, 95% CI
Aydemir 2011a	3	93	15	91	13.4%	0.17 [0.05, 0.61]
Benjamin 2014	8	188	15	173	18.3%	0.47 [0.19, 1.13]
Kaufman 2001	1	50	13	50	7.2%	0.06 [0.01, 0.46]
Kicklighter 2001	2	53	2	50	7.7%	0.94 [0.13, 6.95]
Kirpal 2015	8	38	16	37	16.5%	0.35 [0.13, 0.97]
Manzoni 2007a	7	216	14	106	17.6%	0.22 [0.09, 0.56]
Parikh 2007	16	60	15	60	19.3%	1.09 [0.48, 2.47]
Total (95% CI)		**698**		**567**	**100.0%**	**0.36 [0.19, 0.70]**
Total events	45		90			

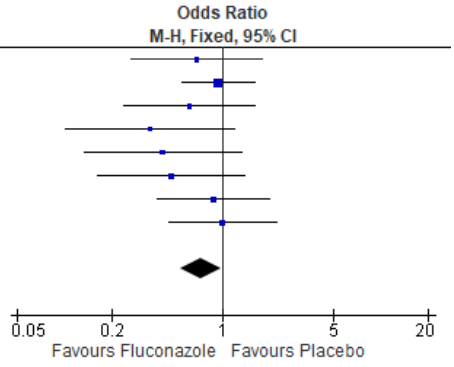
Heterogeneity: Tau² = 0.40; Chi² = 13.43, df = 6 (P = 0.04); I² = 55%
Test for overall effect: Z = 3.05 (P = 0.002)



Mortality (all cause mortality prior to hospital discharge)

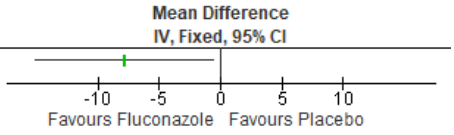
Study or Subgroup	Fluconazole Events	Fluconazole Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Aydemir 2011a	8	93	11	91	9.9%	0.68 [0.26, 1.79]
Benjamin 2014	34	188	33	173	27.5%	0.94 [0.55, 1.59]
Jannatdoust 2015	9	43	15	50	10.7%	0.62 [0.24, 1.60]
Kaufman 2001	4	50	10	50	9.0%	0.35 [0.10, 1.20]
Kicklighter 2001	5	53	10	50	9.1%	0.42 [0.13, 1.32]
Kirpal 2015	7	38	12	37	9.7%	0.47 [0.16, 1.37]
Manzoni 2007a	18	216	10	106	12.0%	0.87 [0.39, 1.96]
Parikh 2007	17	60	17	60	11.9%	1.00 [0.45, 2.21]
Total (95% CI)		**741**		**617**	**100.0%**	**0.73 [0.54, 0.98]**
Total events	102		118			

Heterogeneity: Chi² = 4.71, df = 7 (P = 0.70); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)



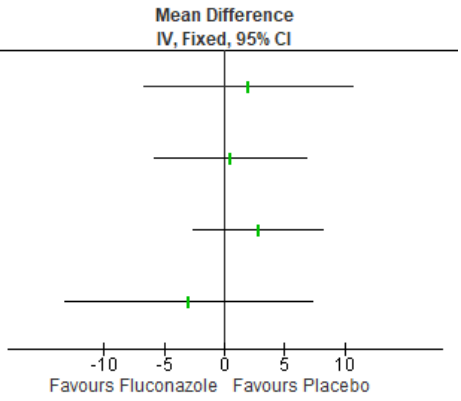
Length of hospital stay (days)

Study or Subgroup	Fluconazole Mean	Fluconazole SD	Fluconazole Total	Placebo/no treatment Mean	Placebo/no treatment SD	Placebo/no treatment Total	Mean Difference IV, Fixed, 95% CI
Jannatdoust 2015	35.16	16.43	43	43.03	19.07	50	-7.87 [-15.08, -0.66]



Neurodevelopmental outcomes (VABS-II scores)

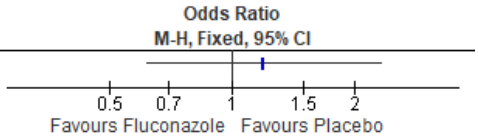
Study or Subgroup	Fluconazole Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.3.1 Communication							
Kaufman 2001 (1)	94.6	14.8	21	92.6	12.6	17	2.00 [-6.71, 10.71]
1.3.2 Daily living skills							
Kaufman 2001	87.9	10.6	21	87.4	9.3	17	0.50 [-5.83, 6.83]
1.3.3 Socialisation							
Kaufman 2001	97.2	9.2	21	94.4	7.9	17	2.80 [-2.64, 8.24]
1.3.4 Motor skills							
Kaufman 2001	92.1	17.8	21	95.1	14.6	17	-3.00 [-13.30, 7.30]



Footnotes
(1) Vineland Adaptive Behavious Scales-II at median age 16 months

Neurodevelopmental impairment (composite score)

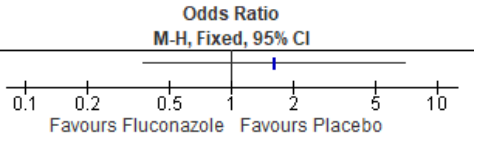
Study or Subgroup	Fluconazole Events	Total	Placebo/no treatment Events	Total	Odds Ratio M-H, Fixed, 95% CI
Benjamin 2014 (1)	27	87	23	84	1.19 [0.62, 2.31]



Footnotes
(1) At least 1 of: 1. Bayley-III cognition composite score <70, 2. Cerebral palsy, 3. Deafness, 4. Blindness at 18-22 month follow-up

Drug-related adverse events (deafness)

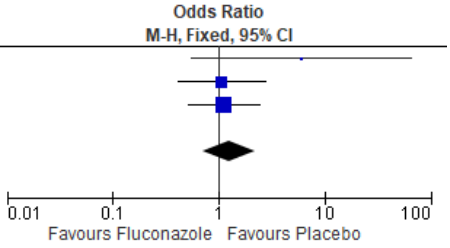
Study or Subgroup	Fluconazole Events	Total	Placebo/no treatment Events	Total	Odds Ratio M-H, Fixed, 95% CI
Benjamin 2014	5	95	3	90	1.61 [0.37, 6.95]



Antifungal resistance

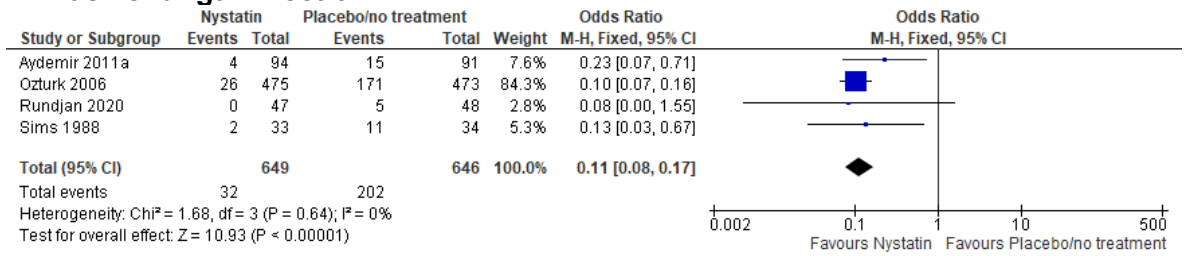
Study or Subgroup	Fluconazole Events	Total	Placebo/no treatment Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Lee 2016	6	12	1	7	2.9%	6.00 [0.54, 66.17]
Manzoni 2006	9	225	9	240	38.8%	1.07 [0.42, 2.74]
Manzoni 2008	18	434	11	295	58.3%	1.12 [0.52, 2.40]
Total (95% CI)		**671**		**542**	**100.0%**	**1.24 [0.70, 2.19]**
Total events	33		21			

Heterogeneity: Chi² = 1.82, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.75 (P = 0.46)

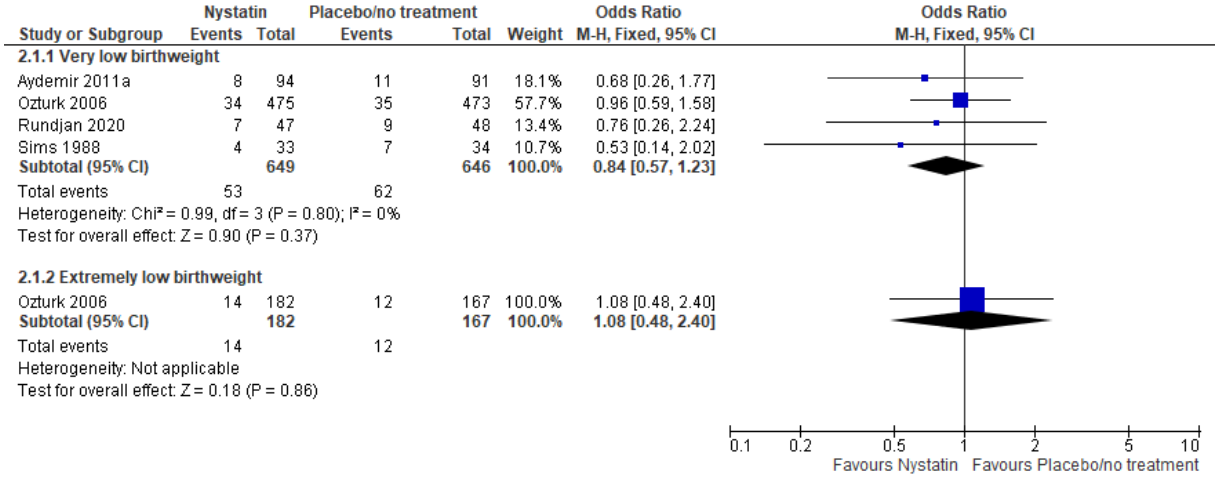


Nystatin v placebo / no treatment

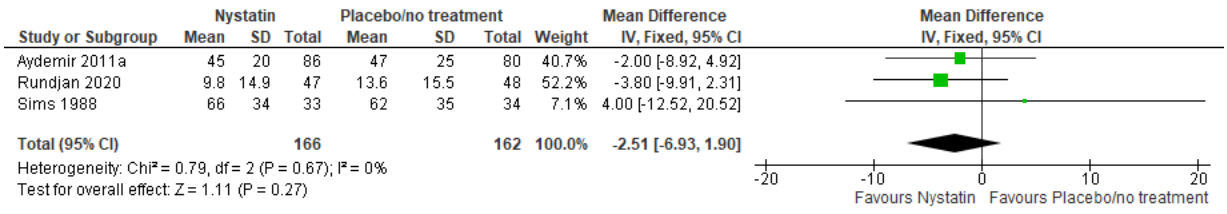
Invasive fungal infection



Mortality (all cause mortality prior to hospital discharge)

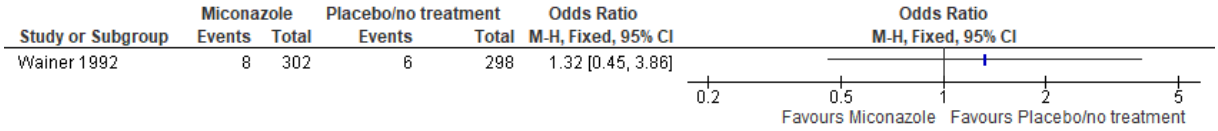


Length of stay in NICU (days)

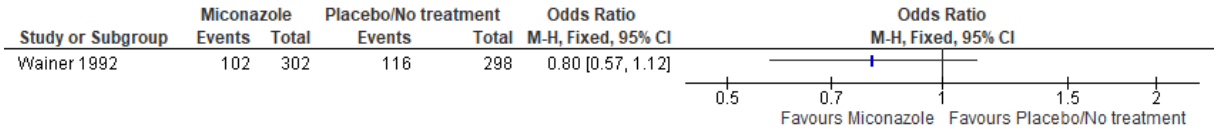


Miconazole v placebo / no treatment

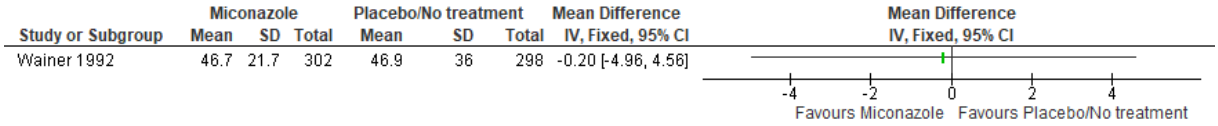
Invasive fungal infection



Mortality (all cause mortality prior to hospital discharge)

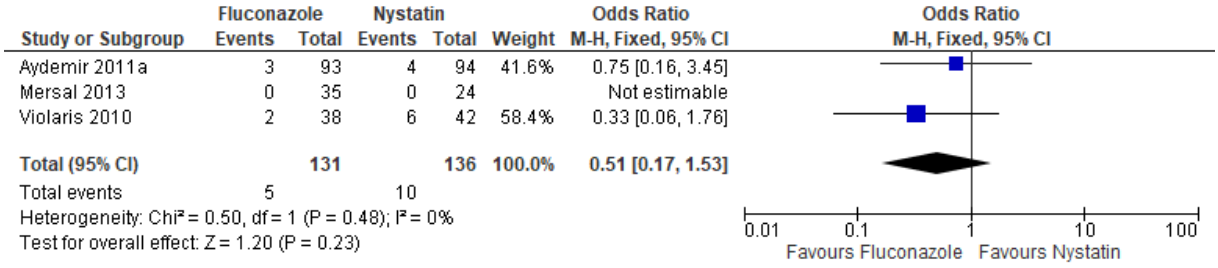


Length of stay in NICU (days)

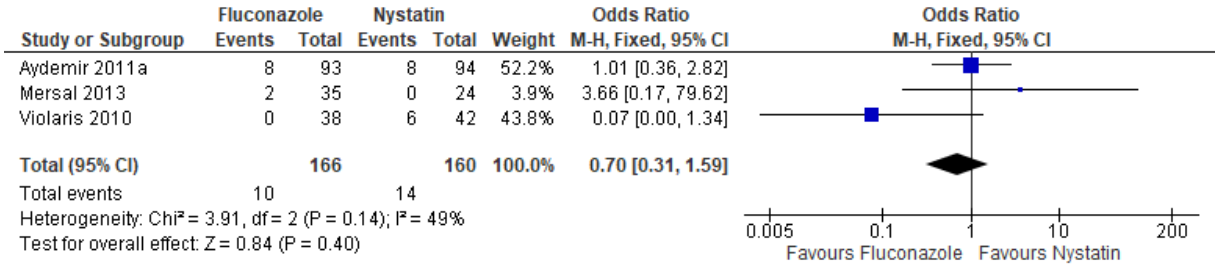


Fluconazole v Nystatin

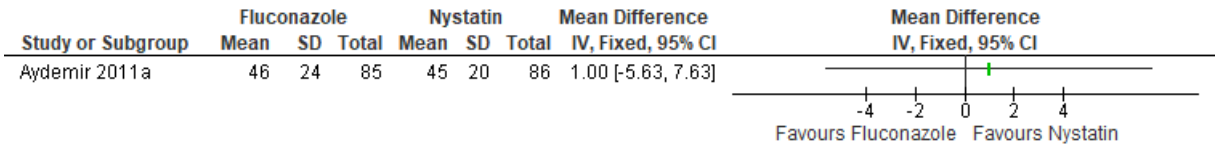
Invasive fungal infection



Mortality (all cause mortality prior to hospital discharge)

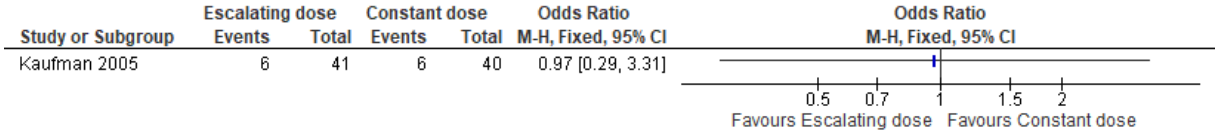


Length of stay (duration of intensive care stay - days)



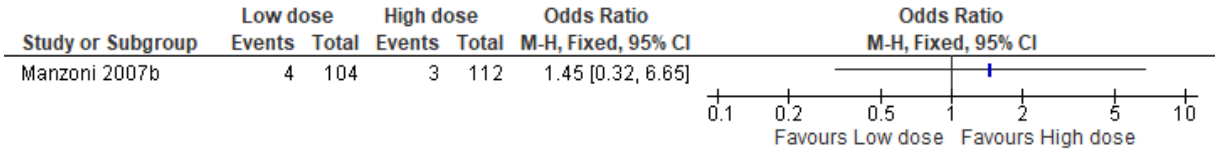
Fluconazole dose comparisons (escalating v constant dose)

Mortality (all cause mortality prior to hospital discharge)

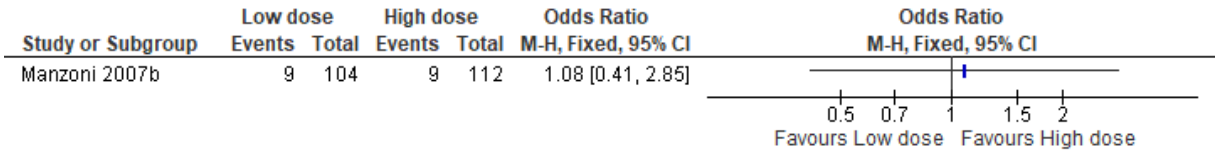


Fluconazole dose comparisons (*3 mg/kg every 2nd day* v *6 mg/kg every 2nd day*)

Invasive fungal infection



Mortality (all cause mortality prior to hospital discharge)



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.

Pair-wise meta-analyses

Fluconazole v placebo/no treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Invasive fungal infection (OR<1 favours fluconazole)									
7	Parallel RCTs	1265	OR 0.36 (0.19, 0.70)	16 per 100	6 per 100 (3, 11)	Not serious	Serious[2]	Very serious[4]	Very low
Mortality (all cause mortality prior to hospital discharge) (OR<1 favours fluconazole)									
8	Parallel RCTs	1358	OR 0.73 (0.54, 0.98)	19 per 100	14 per 100 (10, 19)	Not serious	Not serious	Very serious[4]	Low
Length of hospital stay (days) (MD<0 favours fluconazole)									
1 (Jannatdoust 2015)	Parallel RCT	93	MD -7.87 (-15.08, -0.66)	-	-	Very serious[1]	N/A[3]	Very serious[4]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Neurodevelopmental outcomes (VABS-II scores) (MD<0 favours fluconazole)									
Communication									
1 (Kaufman 2001)	Parallel RCT	38	MD 2.00 (-6.71, 10.71)	-	-	Not serious	N/A[3]	Very serious[4]	Low
Daily living skills									
1 (Kaufman 2001)	Parallel RCT	38	MD 0.50 (-5.83, 6.83)	-	-	Not serious	N/A[3]	Very serious[4]	Low
Socialisation									
1 (Kaufman 2001)	Parallel RCT	38	MD 2.80 (-2.64, 8.24)	-	-	Not serious	N/A[3]	Very serious[4]	Low
Motor skills									
1 (Kaufman 2001)	Parallel RCT	38	MD -3.00 (-13.30, 7.30)	-	-	Not serious	N/A[3]	Very serious[4]	Low
Neurodevelopmental impairment (composite score) (OR<1 favours fluconazole)									
1 (Benjamin 2014)	Parallel RCT	171	OR 1.19 (0.62, 2.31)	27 per 100	33 per 100 (17, 63)	Not serious	N/A[3]	Very serious[4]	Low
Drug-related adverse events (deafness) (OR<1 favours fluconazole)									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
1 (Benjamin 2014)	Parallel RCT	185	OR 1.61 (0.37, 6.95)	3 per 100	5 per 100 (1, 23)	Not serious	N/A[3]	Very serious[4]	Low
Antifungal resistance (OR<1 favours fluconazole)									
3	Retrospective cohorts	1213	OR 1.24 (0.70, 2.19)	4 per 100	5 per 100 (3, 8)	Very serious[1]	Not serious	Very serious[4]	Very low

1. >33% weight of studies at high risk of bias. Quality downgraded 2 levels
2. I^2 between 33.3% and 66.7%. Quality downgraded 1 level
3. Single study. Inconsistency not applicable
4. >33% weight of studies indirectly applicable. Quality downgraded 2 levels

Nystatin v placebo/no treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Invasive fungal infection (OR<1 favours nystatin)									
3	Parallel RCTs	1295	OR 0.11 (0.08, 0.17)	31 per 100	3 per 100 (3, 5)	Serious[1]	Not serious	Very serious[4]	Very low
Mortality (all cause mortality prior to hospital discharge) (OR<1 favours nystatin)									
Very low birthweight subgroup									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
3	Parallel RCTs	1295	OR 0.84 (0.57, 1.23)	10 per 100	8 per 100 (5, 12)	Serious[1]	Not serious	Very serious[4]	Very low
Extremely low birthweight subgroup									
1 (Ozturk 2006)	Parallel RCTs	349	OR 1.08 (0.48, 2.40)	7 per 100	8 per 100 (3, 17)	Serious[2]	N/A[3]	Very serious[5]	Very low
Length of stay in NICU (days) (MD<0 favours nystatin)									
2	Parallel RCTs	328	MD -2.51 (-6.93, 1.90)	-	-	Serious[1]	Not serious	Very serious[4]	Very low

1. >33% weight at moderate risk of bias. Quality downgraded 1 level
2. Single study at moderate risk of bias. Quality downgraded 1 level
3. Single study. Inconsistency not applicable
4. >33% weight indirectly applicable. Quality downgraded 2 levels
5. Single study which is indirectly applicable. Quality downgraded 2 levels

Miconazole v placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Invasive fungal infection (OR<1 favours miconazole)									
1 (Wainer 1992)	Parallel RCT	600	OR 1.32 (0.45, 3.86)	2 per 100	3 per 100 (1, 8)	Very serious[1]	N/A[2]	Very serious[3]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Mortality (all cause mortality prior to hospital discharge) (OR<1 favours miconazole)									
1 (Wainer 1992)	Parallel RCT	600	OR 0.80 (0.57, 1.12)	39 per 100	31 per 100 (22, 44)	Very serious[1]	N/A[2]	Very serious[3]	Very low
Length of stay in NICU (days) (MD<0 favours miconazole)									
1 (Wainer 1992)	Parallel RCT	600	MD -0.20 (-4.96, 4.56)	-	-	Very serious[1]	N/A[2]	Very serious[3]	Very low

1. Single study at high risk of bias. Quality downgraded 2 levels
2. Single study. Inconsistency not applicable
3. Single study which is indirectly applicable. Quality downgraded 2 levels

Fluconazole v nystatin

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Invasive fungal infection (OR<1 favours fluconazole)									
3	Parallel RCT	267	OR 0.51 (0.17, 1.53)	7 per 100	4 per 100 (1, 11)	Serious[1]	Not serious	Very serious[4]	Very low
Mortality (all cause mortality prior to hospital discharge) (OR<1 favours fluconazole)									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
3	Parallel RCT	326	OR 0.70 (0.31, 1.59)	9 per 100	6 per 100 (3, 14)	Serious[1]	Serious[2]	Very serious[4]	Very low
Length of stay in intensive care (days) (MD<0 favours fluconazole)									
1 (Aydemir 2011a)	Parallel RCT	171	MD 1.00 (-5.63, 7.63)	-	-	Serious[1]	N/A[3]	Very serious[4]	Very low

1. >33% weight at moderate risk of bias. Quality downgraded 1 level
2. I^2 between 33.3% and 66.7%. Quality downgraded 1 level. Heterogeneity not explored further because results were examined in more detail in the NMA
3. Single study. Inconsistency not applicable
4. >33% weight indirectly applicable. Quality downgraded 2 levels

Fluconazole dose comparisons (escalating v constant dose)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Mortality (all cause mortality prior to hospital discharge) (OR<1 favours escalating dose)									
1 (Kaufman 2005)	Parallel RCT	81	OR 0.97 (0.29, 3.31)	15 per 100	15 per 100 (5, 50)	Not serious	N/A[1]	Very serious[2]	Low

1. Single study. Inconsistency not applicable
2. Single study which is indirectly applicable. Quality downgraded 2 levels

Fluconazole dose comparisons (3 mg/kg every 2nd day v 6 mg/kg every 2nd day)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Invasive fungal infection (OR<1 favours lower dose)									
1 (Manzoni 2007)	Parallel RCT	216	OR 1.45 (0.32, 6.65)	3 per 100	4 per 100 (1, 18)	Not serious	N/A[1]	Very serious[2]	Low
Mortality (all cause mortality prior to hospital discharge) (OR<1 favours lower dose)									
1 (Manzoni 2007)	Parallel RCT	216	OR 1.08 (0.41, 2.85)	8 per 100	9 per 100 (3, 23)	Not serious	N/A[1]	Very serious[2]	Low

1. Single study. Inconsistency not applicable
2. Single study which is indirectly applicable. Quality downgraded 2 levels

Network meta-analyses

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Quality
Invasive fungal infection							
13	RCT	3,135	See appendix K	Serious[1]	Very serious[2]	Serious[3]	Very low
Mortality (all cause mortality)							
14	RCT	3,287	See appendix K	Serious[1]	Very serious[2]	No Serious	Very low
Length of stay (hospital or neonatal unit)							
5	RCT	1360	See appendix K	Serious[1]	Very serious[2]	No Serious	Very low

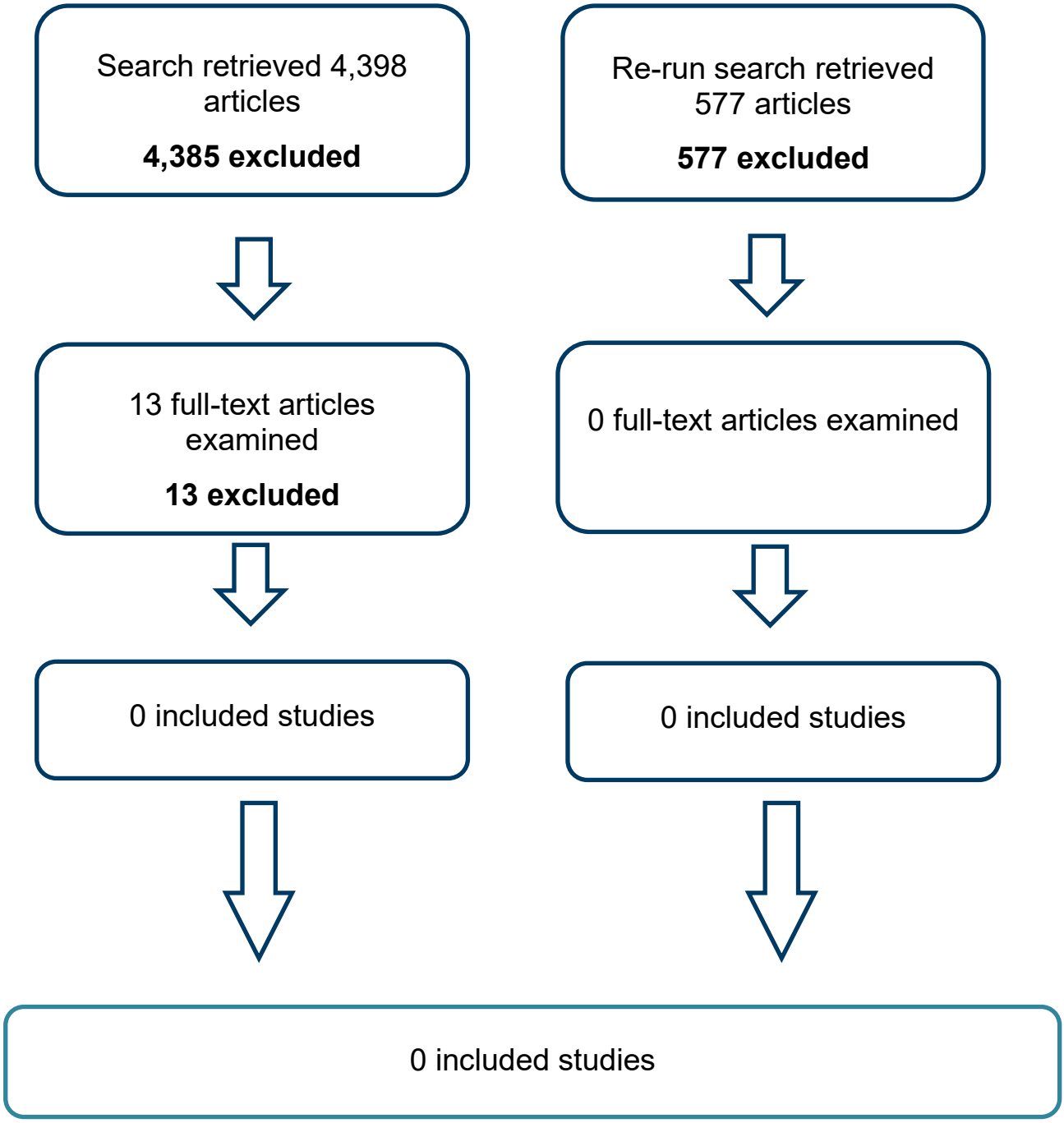
1. >33.3% of studies in the NMA at moderate or high risk of bias. Quality downgraded 1 level
2. >33.3% of studies in the NMA indirectly applicable. Quality downgraded 2 levels

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Quality
3. DIC for a random-effects model lower than the DIC for a fixed-effect model. Between study SD indicates substantial between trial heterogeneity.							

1

2

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence is available as none of the studies in the economic search results were found to be relevant.

Appendix I – Health economic model

I.1 Model overview

The objective of this analysis is to compare the benefits, harms and costs of giving versus not giving antifungals prophylactically in neonates receiving antibiotics for suspected late onset infection.

I.1.1 Population(s)

The target population in the model is neonates who are receiving an antibiotic treatment regimen for suspected late onset infection.

I.1.2 Interventions

There are 2 antifungal treatments for which the clinical review found evidence. Therefore, the model assesses 3 mutually exclusive options:

1. No antifungal prophylaxis
2. Fluconazole
3. Nystatin

In the clinical review, there was some evidence exploring the effectiveness of a fourth antifungal agent, miconazole. However, this was entirely drawn from a single RCT dating from 1992 (Wainer et al. 1992), and the committee advised that miconazole is not used for this indication in current practice. For this reason, we did not include it among the modelled interventions.

In addition, in planning the analysis, the committee advised that some clinicians are interested in using micafungin, a newer antifungal that is associated with higher acquisition costs than fluconazole or nystatin. However, there was no evidence on the efficacy of micafungin in this indication, so we were unable to provide an analysis of its cost effectiveness.

I.1.3 Type of evaluation, time horizon, perspective

The analysis measures outcomes in quality-adjusted life years (QALYs). We express the incremental cost-effectiveness ratio (ICER) as a cost per QALY.

The model has a lifetime horizon, to reflect all important differences in costs and outcomes between the interventions being compared. However, all relevant transitions occur within the neonatal period; the remainder of the model solely calculates the lifelong impact of infections.

The analysis was conducted from the perspective of NHS and Personal Social Services (PSS) in the UK.

I.1.14 Discounting

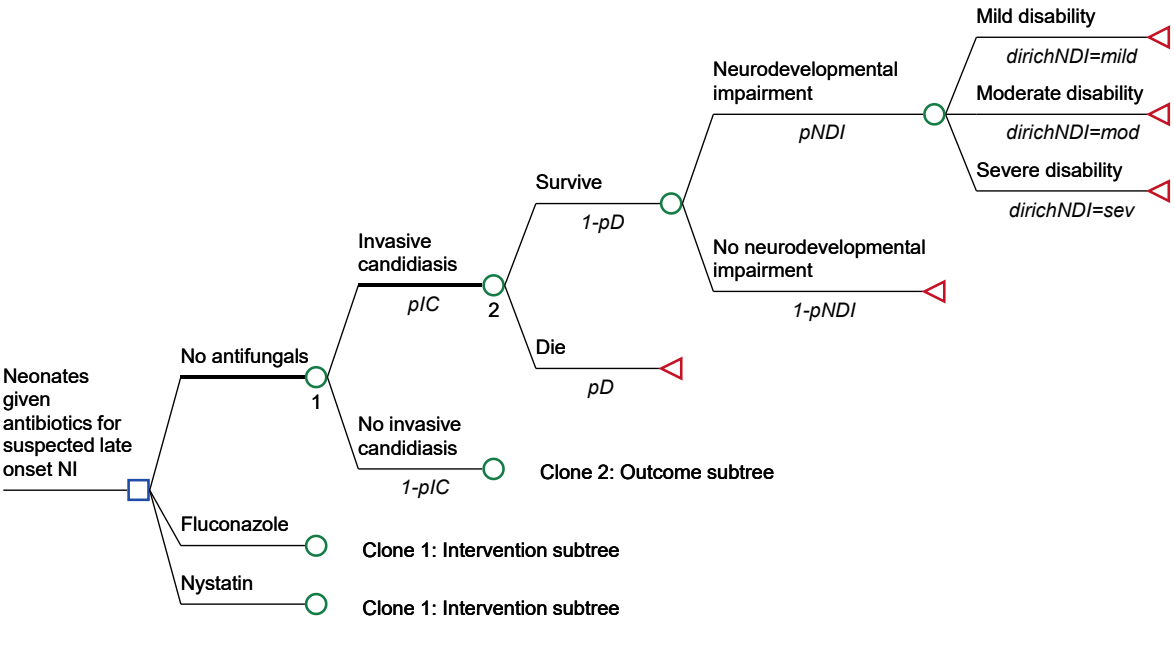
The analysis discounts all costs and QALYs at a rate of 3.5% per year, as required by Developing NICE guidelines: the manual .

I.2 Model structure

We constructed a decision-tree model in Microsoft Excel. Figure HE001 provides a schematic depiction of the model structure. We designed the model structure to reflect the clinical outcomes associated with invasive candidiasis. The committee advised that antifungal therapy is associated with negligible short- or long-term harms for the baby; the main reasons why clinicians might not use them are (a) cost and (b) minimising antimicrobial prescribing, out of concern for cultivating resistance in fungal pathogens. We account for the former in our model. The impact of microbial resistance is not practicably quantifiable, especially as the clinical review found very little evidence about how the use of antifungals in the population of interest might influence it. However, the committee took this factor into account qualitatively when discussing the evidence (see 1.1.10 The committee's discussion and interpretation of the evidence, above).

As a result, the model simply aims to estimate the probability of invasive candidiasis with and without prophylaxis, as well as the lifetime consequences for affected neonates. Through a series of conditional probabilities, all simulated babies end in 1 of 5 categories: surviving with no neurodevelopmental impairment, surviving with mild neurodevelopmental impairment, surviving with moderate neurodevelopmental impairment, surviving with severe neurodevelopmental impairment and dead. Invasive candidiasis is associated with higher risk of death and neurodevelopmental impairment. The model considers the impact of these outcomes measured in costs and QALYs.

Figure HE001 provides a schematic depiction of the model structure.



Probability of invasive candidiasis varies according to prophylaxis strategy (fluconazole -v- nystatin -v- none). Probability of death and probability of neurodevelopmental impairment vary according to invasive candidiasis status (yes -v- no).

Figure HE001: Model structure

I.3 Model parameterisation

I.3.1 General approach

I.3.1.1 Identifying sources of parameters

With the exception of probability of invasive candidiasis, which came from the systematic review conducted for this research question (see below), we identified parameters through informal searches that aimed to satisfy the principle of 'saturation' (that is, to 'identify the breadth of information needs relevant to a model and sufficient information such that further efforts to identify more information would add nothing to the analysis' [Kaltenthaler et al., 2011]). We conducted searches in a variety of general databases, including Medline (via PubMed), the Cochrane Database of Systematic Reviews and GoogleScholar.

When searching for quality of life, resource-use and cost parameters in particular, we conducted searches in specific databases designed for this purpose, the CEA (Cost-Effectiveness Analysis) Registry and the NHS Economic Evaluation Database (NHS EED) for example.

We asked the committee to identify papers of relevance. We reviewed the sources of parameters used in the published economic analyses identified in our systematic reviews for all review questions; during the reviews, we also retrieved articles that did not meet the formal inclusion criteria, but appeared to be promising sources of evidence for our model. We studied the reference lists of articles retrieved through any of these approaches to identify any further publications of interest.

I.3.1.2 Selecting parameters

Our overriding selection criteria were as follows:

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

I.3.2 Baseline clinical data and natural history

I.3.2.1 Baseline risk of invasive fungal infection

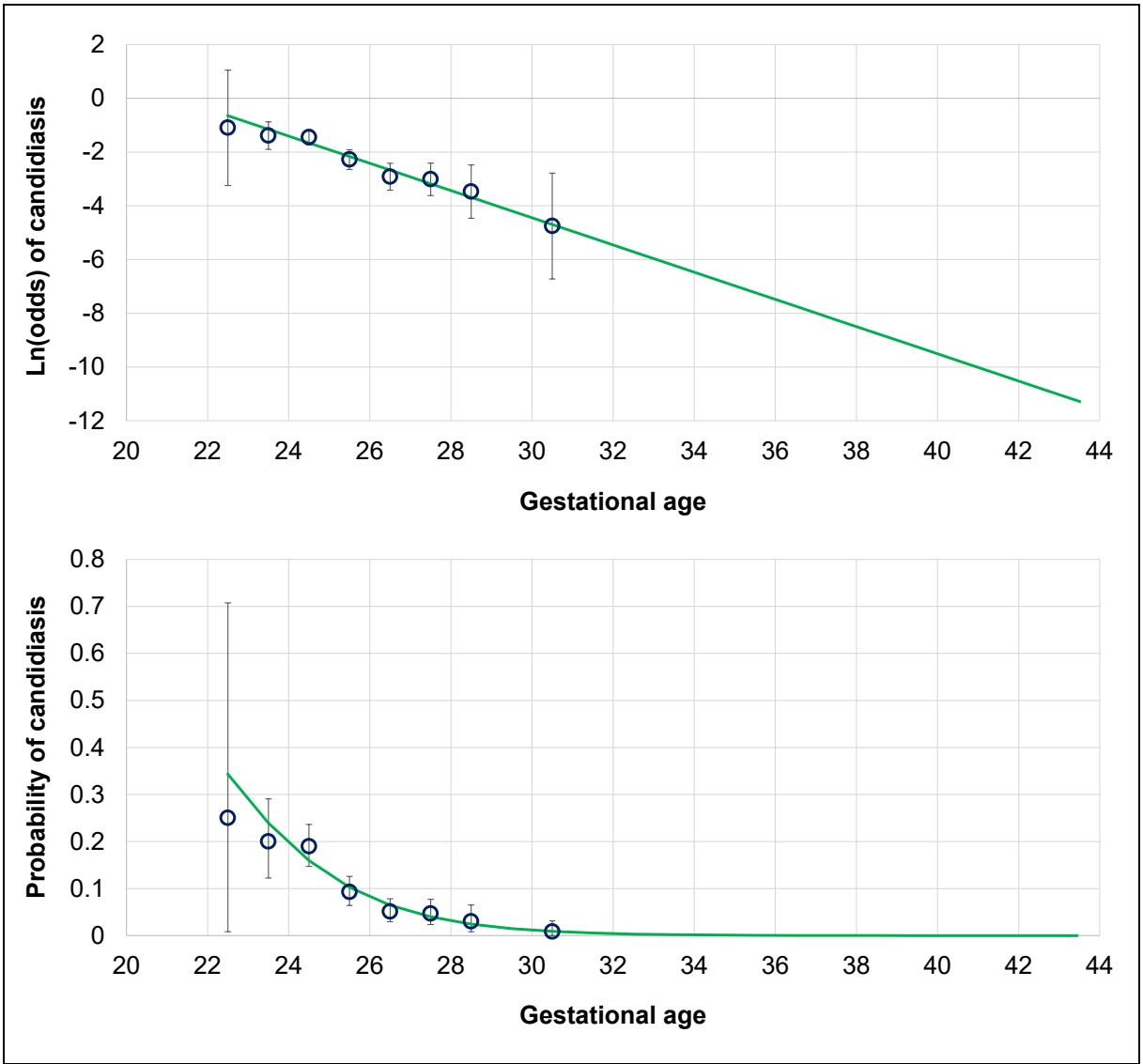
The underlying probability that a neonate will contract an invasive fungal infection is central to this model (as it is to current decision-making, which tends to reserve prophylaxis for infants perceived to be at highest risk; Kaguelidou et al. 2012).

I.3.212 Risk factors for invasive fungal infection

In any individual case, the absolute probability of invasive candidiasis is dependent on multiple factors, key among which are gestational age and/or birthweight. From the perspective of our decision problem, which focuses on babies receiving antibiotics for suspected bacterial infection, it may also be critical that exposure to broad-spectrum antibiotics is a consistent risk factor for candidiasis (Cotten et al. 2006, Benjamin et al. 2010).

To quantify the extent to which gestational age and exposure to broad-spectrum antibiotics modify the risk of invasive candidiasis, we use evidence from a large, prospective, observational cohort study of extremely low-birthweight infants in the USA (Benjamin et al. 2010). Although these data come from a different setting to our decision problem, where absolute rates of candidiasis are likely to be different (see below) we only use them to estimate the extent to which gestational age is a relative modifier of risk, which is much more likely to generalise across settings. It is also a positive benefit, for our purposes, that this study reports somewhat historical practice (recruitment 2004–07), because it predates the widespread use of antifungal prophylaxis. This means it is well suited to estimate baseline risk before applying the treatment effects from our review.

Figure HE002 shows the relationship between gestational age and chance of invasive candidiasis. As shown in the top panel, the data form a strongly linear pattern on a logistic (log-odds) scale; this gives us somewhat more confidence if we want to extrapolate beyond the range of the observed data.



Top panel shows data on log-odds scale with linear weighted regression; bottom panel shows same data translated to natural probability scale

Figure HE002: Baseline risk of infection according to gestational age

We calculated the regression line shown in Figure HE002 by undertaking a weighted logistic regression of gestational age on probability of candidiasis. Table HE001 shows the results. It suggests that each week of gestational age is associated with around a 40% reduction in odds of invasive candidiasis.

Table HE001: Influence of gestational age on risk of candidiasis

	Logistic scale		Odds ratio (natural scale)		*p*
	Estimate	SE	Estimate	95%CI	
Intercept	10.742	1.728			<0.001
Gestational age (per week)	-0.506	0.068	0.603	0.525 to 0.686	<0.001

Weighted logistic in regression in R 4.0.2: `glm(formula = n/N ~ GA, family = binomial, weights = N)`, *where N is the number of babies at each gestational age (GA) and n is the number of cases of candidiasis observed in that category.*

We generally only use the slope from this model (as described below); however, in sensitivity analysis where the Benjamin et al. (2010) data are used to estimate absolute as well as relative likelihood of candidiasis, it is necessary to account for correlation between the intercept and slope of the regression in probabilistic sampling – the relevant covariance estimate is −0.118.

We use the same study to estimate the relative effect of exposure to broad-spectrum antibiotics on probability of candidiasis. Benjamin et al. (2010) report an odds ratio of 1.98 (95%CI 1.37 to 2.86) for this factor, which is similar to an earlier estimate from the same group of authors (2.16 [95%CI 1.42 to 3.28]; Cotton et al. 2006). However, it would not be appropriate to apply this effect modifier directly to the gestation-specific estimates calculated above, because those comprise a mixture of infants with and without exposure to broad spectrum antibiotics. We need to adjust for this to arrive at a best estimate of event-rates with and without the exposure.

To do this, we note that the observed odds of experiencing the event (o_{all}) are a combination of the odds with the exposure (o_{BSA}) and odds without the exposure (o_{noBSA}) weighted according to the probability of exposure (p_{BSA} – 692 of 6,777 cultures [10.2%] in Benjamin et al. 2010 came from infants who had received broad-spectrum antibiotics):

$$o_{all} = o_{BSA}p_{BSA} + o_{noBSA}(1 - p_{BSA}) \quad \textbf{(1)}$$

And the relation between the exposed and unexposed odds is defined by our odds ratio ($OR_{BSA\text{-}v\text{-}noBSA}$):

$$o_{BSA} = o_{noBSA}OR_{BSA\text{-}v\text{-}noBSA} \quad \textbf{(2)}$$

These 2 expressions may be treated as simultaneous equations and rearranged as:

$$o_{noBSA} = \frac{o_{all}}{(1 - p_{BSA}) + p_{BSA}OR_{BSA\text{-}v\text{-}noBSA}} \quad \textbf{(3)}$$

Once we have a result for the unexposed, we plug it into equation (2) to estimate odds in the exposed. Figure HE003 shows the results of these calculations.

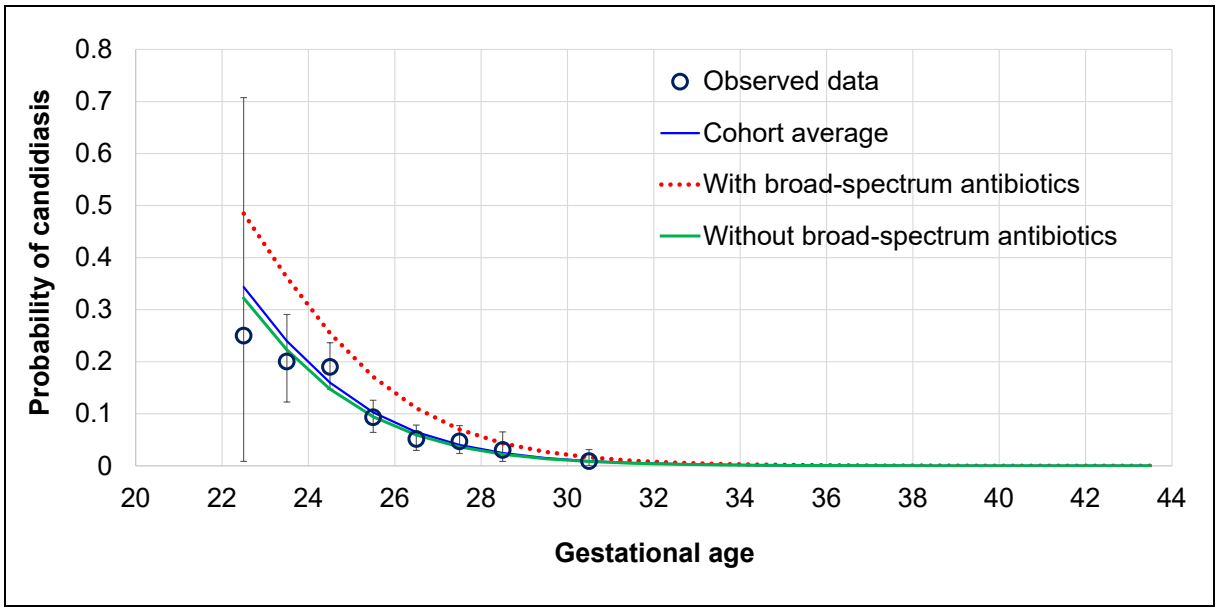


Figure HE003: Baseline risk of infection according to gestational age and exposure to broad-spectrum antibiotics

I.3.2.3 Absolute probability of invasive fungal infection

All the calculations above describe our approach to modelling risk factors for candidiasis – that is, the extent to which lower gestational age and exposure to broad-spectrum antibiotics make fungal infections **more** likely. However, we can apply these relative effects to any absolute probability of candidiasis, and we should rely on a base-case estimate that seeks to reflect our decision space as closely as possible.

Notably, the absolute rate of invasive candidiasis in Benjamin et al. (2010), the US study from which we draw our estimates of relative effects, is quite a lot higher than contemporaneous UK investigators have observed. Benjamin et al. (2010) report an incidence of 9.0% among extremely low-birthweight infants born 2004–07, whereas the rate of invasive fungal infection in the same group in the UK in 2004–10 was 1.88% (Oeser et al. 2014). However, the latter figure includes a nontrivial proportion of experience from units who adopted routine antifungal prophylaxis during the study. This is unhelpful, for our purposes, because our model aims to distinguish outcomes with and without prophylaxis and these overall data conflate the 2. Happily, Oeser et al. also report the rate of candidiasis observed in 4 units before the implementation of prophylaxis policies – a rate of 3.15% among extremely low-birthweight infants. We use this number as our base-case estimate of absolute probability of invasive fungal infection without prophylaxis.

To fit the gestation-specific model from I.3.2.2 to this underlying expectation, we assume that extremely low birthweight corresponds, on average, to a gestational age of 27 weeks or less (this is the gestational age at which both male and female UK newborns achieve a median birthweight of 1,000 g; Norris et al. 2017). First we calculate odds of infection in the lowest category (22 weeks' gestation, o_{22}) as a function of the overall odds ($o_{22:27}$), the per-gestational-week odds ratio (OR) and the relative frequency of births at each gestational age i (n_i, taken from ONS Birth characteristics in England and Wales 2018):

$$o_{22} = o_{22:27} \div \sum_{i=22}^{i=27} e^{OR(i-22)} \frac{n_i}{\sum_{j=22}^{j=27} n_j} \quad \textbf{(4)}$$

Then we can estimate odds for each subsequent gestational age by applying the odds ratio per week of gestation (OR – that is, the exponentiated coefficient from Table HE001). That is, for any given gestational age x, the odds of invasive fungal infection (o_x) are:

$$o_x = o_{22} OR^{(x-22)} \quad \textbf{(5)}$$

Finally, we convert our calculated odds into probabilities. Figure HE004 shows the resulting estimates (note different *y*-axis scale compared with Figure HE002 and Figure HE003).

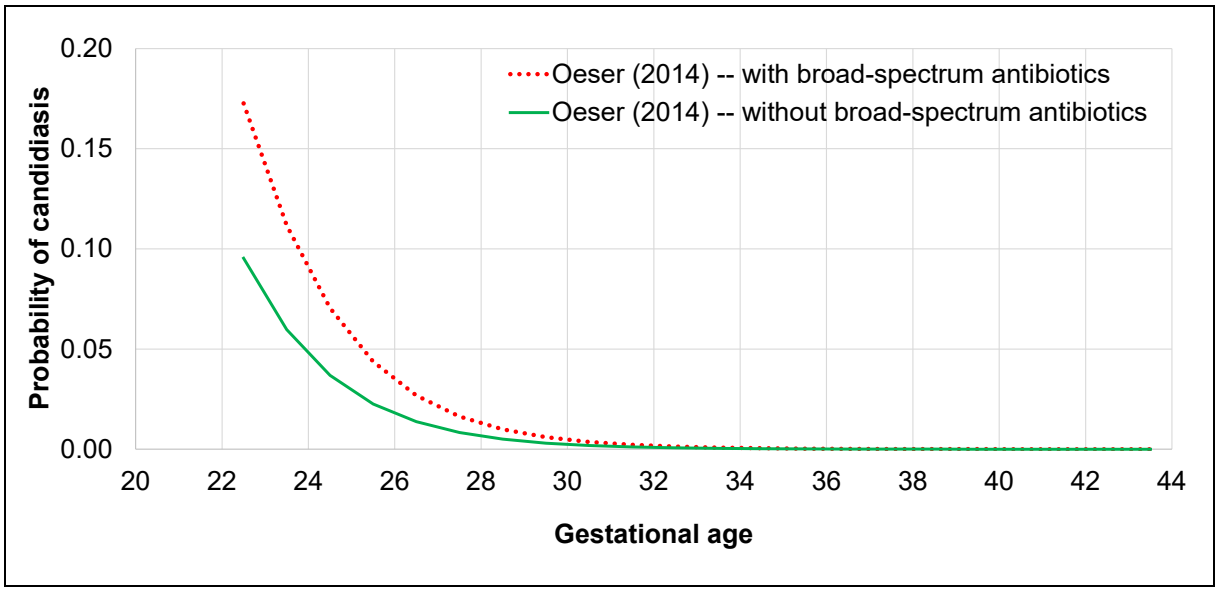


Figure HE004: Baseline risk of infection according to gestational age and exposure to broad-spectrum antibiotics, fitted to UK-specific incidence data

We also explore the impact of calibrating these curves to alternative absolute incidence rates, as shown in Table HE002.

Table HE002: Absolute risk of invasive fungal infection

	Incidence %	Equivalent rate per 1,000 live births	Population
Base case			
Oeser et al. (2014)	0.03150[a]	0.187	England; extremely low-birthweight babies not receiving antifungal prophylaxis
Alternative value (scenario analysis)			
Cailes et al. (2018)	0.00042 (151/355,901[b])	0.424	England and Wales; all live births
Benjamin et al. (2010)	0.0904 (137/1515)	0.841	USA; extremely low-birthweight babies

(a) Denominator not reported; in the absence of evidence, we assume the same coefficient of variation as reported in Benjamin et al. (2010), leading to a SE of 0.0026 (95%CI 0.0267 to 0.0367)
(b) Cailes et al. 2018 did not directly report the total births for the population. The value 355,901 was obtained by dividing their reported total number of infections (bacterial and fungal) by their reported incidence of infection per 1000 live births: 2171/0.0061=355,901.

I.3.214 Additional risk factors for invasive fungal infection

The same study that provides our relative effect of exposure to broad-spectrum antibiotics on probability of candidiasis also provides relative effects for four other factors on probability of candidiasis, detailed in Table HE003 (Benjamin et al. 2010).

Table HE003: Sequelae of candidiasis (from Benjamin et al. 2006)

Effect	Adjusted odds ratio	P value
Central catheter	1.94 (1.17 to 3.21)	0.0098
IV lipid emulsion	1.66 (0.98 to 2.81)	0.0596
Endotracheal tube	1.58 (1.07 to 2.35)	0.0226
Antenatal antibiotics	1.40 (0.97 to 2.03)	0.0747

The model is built in such a way that multiple effects can be considered at one time, that is, we can simulate a cohort that has had a central catheter placed, received IV lipid emulsion but has not had an endotracheal tube and has not received antenatal antibiotics. However, none of these effects are included in the base case of the model as, in line with the review question, our main focus is on the effects of broad-spectrum antibiotics (in conjunction with gestational age). Our exploration of these additional risk factors is restricted to scenario analyses.

I.3.3 Treatment effects

The model's only basic effectiveness parameter is relative probability of invasive fungal infection, with other outcomes conditional on this assumed independent of antifungal prophylaxis strategy (in other words: antifungal prophylaxis changes the probability of fungal infection, but does not affect the consequences of any infections that arise).

As the RCTs also provide empirical data on mortality with each prophylaxis approach, an alternative model structure would be to use these data to model probability of death directly. This could be **instead** of directly modelling infection-rates; however, it would not be appropriate to ignore non-fatal infections, which may be associated with substantial, lifelong costs and consequences. A further alternative is to model treatment-dependent mortality **as well as** fungal infection-rates in a single synthesis. A simple approach to this would be to assume conditional dependence between the outcomes. However, this would be structurally inappropriate for these data: babies develop fungal infections without dying and babies die without developing fungal infections (this fact is reflected in the RCT data, some of which have more deaths than infections whereas others have more infections than deaths). A more sophisticated 'chain of evidence' approach has been demonstrated in broadly analogous data structures (Eddy 1989, Ades 2003, Dias et al. 2018). In this approach, it might be possible to model observed deaths conditional on infection by using external data on the probability of death given infection and simultaneously estimating treatment effects for probability of infection. We undertook preliminary investigation of this approach; however, existing methods require modelling on an absolute risk scale (Dias et al. 2018) or strong assumptions about baseline probabilities (Ades 2003). These are substantial limitations, from the perspective of our analysis, which is critically dependent on varying baseline probabilities of infection, which may be very low for some neonates (e.g. a term baby admitted from home) and very high for others (e.g. an extremely low birthweight infant with a central line receiving broad-spectrum antibiotics). Therefore, we concluded that a simple approach relying solely on the fungal infection NMA would provide outputs that are much more usable for decision-making.

Nevertheless, we used the mortality NMA as a point of validation for the outputs of our model, to check that the predictions of our simple approach are not inconsistent with the observed mortality data.

Similarly, there are some empirical data on length of hospital stay that the clinical review presents in an NMA (see Appendix K). However, this is based on limited data from a minority of included RCTs, with the result that NMA outputs have wide credibility intervals. Therefore, we do not use these data directly (though, again, we check our model's outputs against this evidence as part of our validation).

I.3.31 Invasive fungal infection

As part of the review of clinical evidence, we undertook network meta-analysis (NMA) to estimate the relative effects of prophylaxis on incidence of infection. Full details are provided in Appendix K.

The relevant model inputs are shown in Table HE004.

Table HE004: OR of infection

	Fluconazole	Nystatin
Log odds ratio		
Posterior mean	-1.373	-1.815
SD	0.386	0.503
OR (95%CrI) on natural scale	0.253 (0.114, 0.525)	0.163 (0.060, 0.446)
Correlation matrix		
Fluconazole	1	0.182
Nystatin	0.182	1

I.3.32 Consequences of infection

Neurodevelopmental sequelae

In our model, neonates with invasive candidiasis have an increased risk for neurodevelopmental impairment. The model estimates probability of NDI as a 2-stage process: first, we specify the absolute probability of NDI for a neonate who does not experience invasive candidiasis; then we apply a relative effect to estimate the extent to which experiencing fungal infection increases the chance of NDI.

We use data from a paper that reports rates of cerebral palsy in the North of England by gestational age as a proxy for NDI (Glinianaia et al. 2011). Using these data, we calculate a regression line shown in Figure HE005 by undertaking a weighted logistic regression of gestational age on probability of cerebral palsy. Table HE005 shows the results. It suggests that each week of gestational age is associated with around a 26% reduction in odds of cerebral palsy.

Table HE005: Influence of gestational age on risk of neurodevelopmental impairment

	Logistic scale		Odds ratio (natural scale)		*p*
	Estimate	SE	Estimate	95%CI	
Intercept	5.724	0.376			<0.001
Gestational age (per week)	-0.302	0.010	0.739	0.725 to 0.754	<0.001

Weighted logistic in regression in R 4.0.2: `glm(formula = n/N ~ GA, family = binomial, weights = N)`, *where N is the number of babies at each gestational age (GA) and n is the number of cases of cerebral palsy observed in that category.*

Using this regression line, we then apply our relative effect, which is quantified using data from Benjamin et al. (2006). This prospective cohort study reports incidence rates for impairment in extremely low birthweight neonates who survived to neurodevelopmental follow up 18–22 months of age, distinguishing between those who experienced neonatal invasive candidiasis and those who did not. The authors separated reported values into 3 categories: candidaemia, candida meningitis and no candida. We combined the data for candidaemia and candida meningitis to obtain values for any candidiasis. Table HE006 shows the resulting model inputs.

Table HE006: Sequelae of candidiasis (from Benjamin et al. 2006)

	Incidence of outcome – n/N (%)		
Sequela	Candidiasis	No candidiasis	Odds ratio
Any neurodevelopmental impairment	95/167 (56.9%)	962/2686 (35.8%)	2.36 (1.72 to 3.24)

We then use our regression line to calculate the odds of NDI without invasive candidiasis. In order to calculate the odds of NDI with invasive candidiasis, we apply our relative effect from Table HE006. The probability of NDI by gestational age both with and without invasive candidiasis can then be obtained using a standard odds-to-probability conversion. Figure HE005 illustrates these results.

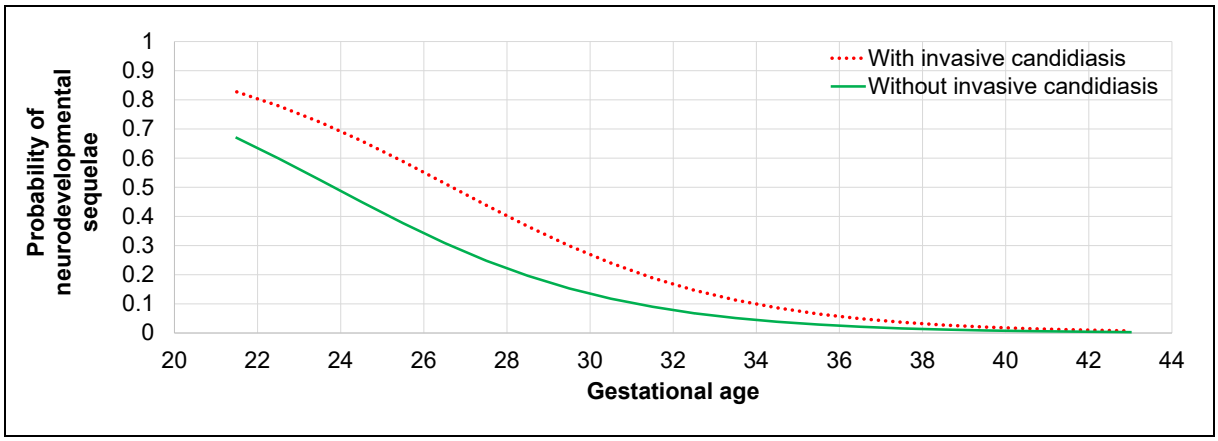


Figure HE005: Probability of NDI with and without invasive candidiasis

Benjamin et al. (2006) also detail incidence of specific impairments, including cerebral palsy, hearing impairment and visual impairment. However, it would be difficult to use these data in our model, as there is clearly some overlap between outcomes (they are not mutually exclusive, but there are no data as to how multiple conditions coexist), and it would also require us to build lifetime models estimating lifetime costs and QALYs associated with a range of outcomes for which data are likely to be sparsely available. Therefore, the committee decided that it was an acceptable simplification for the model to consider

neurodevelopmental impairment as an overarching category, which could then be stratified by severity using data from elsewhere (see below).

Severity of disability

In order to calculate the severity of disability, conditional on some degree of impairment being experienced, we used the proportions of mild, moderate and severe disability observed in a prospective, population-based cohort study of extremely premature babies in England (Petrou et al. 2013). This has the advantage of being UK-specific evidence drawn from the same cohort we use to estimate the costs and quality of life impacts with which neurodevelopmental impairment is associated (see below). Although this cohort is not specific to babies experiencing disability following infection, the committee was content to assume that those experiencing some degree of neurodevelopmental impairment in this group would have a similar spectrum of long-term disability as those experiencing some degree of neurodevelopmental impairment secondary to neonatal invasive candidiasis.

To explore the impact of this decision, in sensitivity analysis, we used the same source we used in our model simulating management of preterm, prelabour rupture of membranes (Colbourn et al. 2007; see evidence review C). These data reflect the probability of long-term impairment among infants experiencing some degree of disability following various types of bacterial infection (in turn, this is the same NIHR-funded evidence synthesis used to estimate sequelae in CG149). Table HE007 summarises the range of values explored.

Table HE007: Risk of disability due to disability (from Colbourn et al. 2007)

	Severity of impairment						
	Reported data including no impairment % (95%CI)				Conditional on some degree of impairment[a] % (n/N)		
	None	Mild	Moderate	Severe	Mild	Moderate	Severe
Base case (Petrou et al. 2013)							
Extremely premature babies	–	–	–	–	59.7% (117/196)	29.1% (57/196)	11.2% (22/196)
Alternative values (Colbourn et al. 2007)							
Early-onset meningitis	61.4% (53.5, 69.2%)	19.6% (13.6, 26.4%)	12.9% (8.1, 18.7%)	6.1% (2.9, 10.4%)	50.8%	33.4%	15.8%
Late-onset meningitis	52.3% (43.7, 60.9%)	19.7% (13.4, 26.8%)	14.3% (8.9, 20.9%)	13.6% (8.4, 20.1%)	41.4%	30.0%	28.6%
Bacteraemia no meningitis	74.6% (64.1, 83.8%)	4.5% (1.1, 10.0%)	13.9% (7.2, 22.2%)	7.0% (2.3, 13.8%)	17.7%	54.7%	27.6%

(a) Colbourn et al. (2007) report posterior estimates from their synthesis model across 4 categories (including no impairment). We need the probability of any given degree of impairment conditional on some degree of impairment – e.g. for LOGBS meningitis, the conditional probability of severe impairment is 0.136 ÷ (1−0.523) = 0.286. To ensure that coherence is maintained is probabilistic analysis, we sample from a Dirichlet distribution across all 4 categories and then calculate the conditional probabilities in every probabilistic iteration of the model.

I.3.323 Mortality

Death related to invasive candidiasis

The model estimates probability of death as a 2-stage process: first, we specify the absolute probability of death for a neonate who does not experience invasive candidiasis; then we apply a relative effect to estimate the extent to which experiencing fungal infection increases the chance of mortality.

We take the absolute probability of death from ONS data – the 'Infant mortality (birth cohort) tables in England and Wales' for which the most current data details outcomes from 2017. Because this is a large, nationwide dataset and candidaemia is an uncommon cause of death, we assume that this can be used as a baseline without adjustment. This dataset allows us to calculate risk of death as a function of gestational age. Figure HE006 illustrates these data.

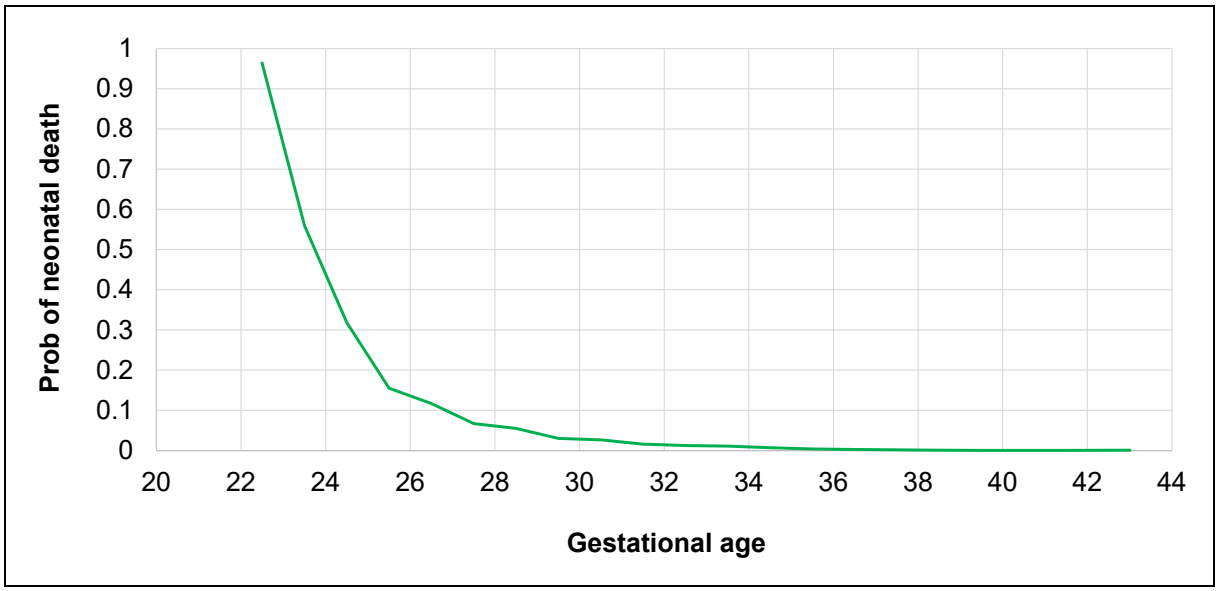


Figure HE006: Baseline probability of death

Our estimate of the extent to which invasive candidiasis raises the chance of neonatal death comes from Benjamin et al. (2006), the same study we use for probability of neurodevelopmental impairment. Table HE008 shows the data.

Table HE008: Sequelae of candidiasis (from Benjamin et al. 2006)

Sequela	Incidence of outcome – n/N (%)		Relative effect (odds ratio)	Absolute effect (risk difference)
	Candidiasis	No candidiasis		
Death	101/320 (31.6%)	703/4259 (16.5%)	2.33 (1.82 to 2.99)	0.151 (0.098 to 0.203)

We can apply this effect in 2 ways: on a relative scale (invasive candidiasis more than doubles a neonate's odds of death) or on an absolute one (invasive candidiasis raises a neonate's probability of death by 15 percentage-points). Figure HE007 illustrates the difference. The committee noted that, for very premature neonates (who have by far the highest risk of developing candidiasis; see I.3.2), there is not much difference between the 2 approaches; it is only as the baseline risk of neonatal death recedes that the absolute approach provides a much higher estimate of excess mortality.

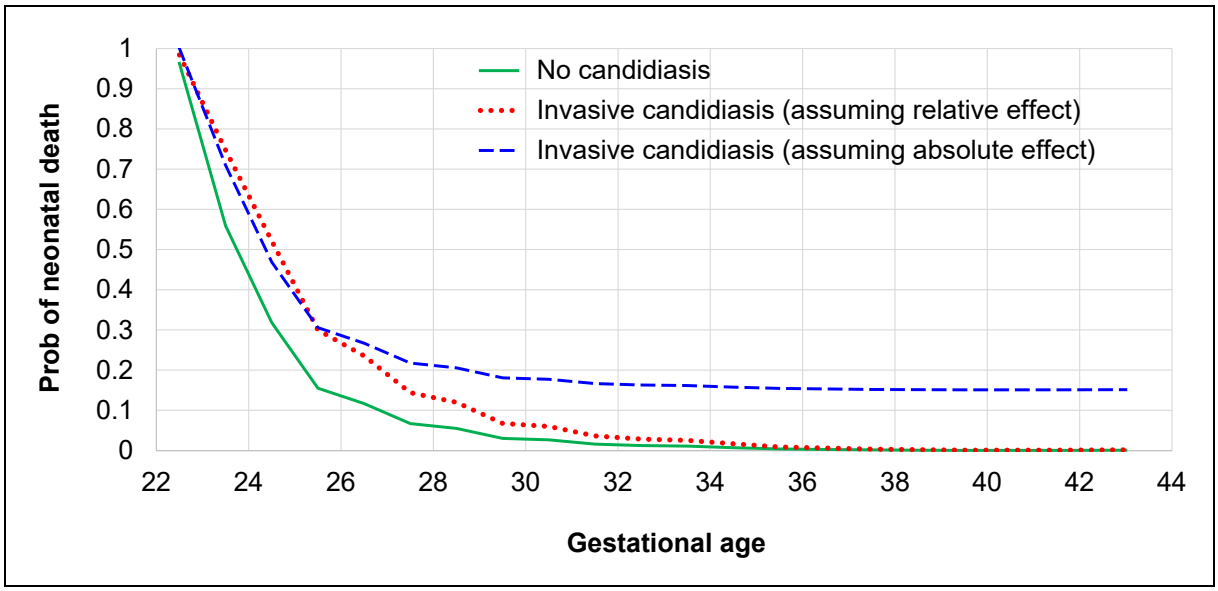


Figure HE007: Probability of death with and without invasive candidiasis

We use the relative effect in our base case. There is some evidence that, while candidiasis is associated with conspicuous excess mortality in extremely low-birthweight infants, a similar association cannot be detected in neonates with higher birthweights (Zaoutis et al. 2007). We also note that 100% of the deaths associated with fungal infection observed in the UK neonatal infection surveillance network happened in extremely low-birthweight infants (Oeser et al. 2014). These would be unlikely findings if candidiasis were associated with a constant, absolute increase in mortality. Nevertheless, the absolute effect assumption represents a useful upper bound to our uncertainty, so we explore the approach in sensitivity analysis.

As noted in I.3.3, we also had access to the NMA from the clinical review estimating the direct mortality effects of antifungal prophylaxis. For the reasons discussed in I.3.3, we did not use these data as inputs to our analysis, but we checked the outputs of our model against them, to validate the predictions the model makes.

Expected lifespan of neonatal survivors

We also need an estimate of expected lifespan to estimate the costs and effects for neonates sustaining lifelong morbidity. For this, we emulate the approach used in a recent cost-effectiveness analysis (Grosso et al. 2019). This approach takes the probability of death from 2016–18 UK life tables (ONS 2019) and inflates it using hazard ratios from Reid et al. (2012) to estimate the additional risk of death due to NDI. Table HE009 shows the resulting estimates.

Table HE009: Expected lifespan of neonatal survivors (using Reid et al. 2012)

Severity of impairment	Hazard ratio (95%CI)	Equivalent life expectancy at birth (using 2016–18 UK lifetables)		
		Undiscounted	Discounted	
			3.5% / year	1.5% / year
Motor impairment				
None		81.27	27.42	46.96
Mild	1.00	81.27	27.42	46.97
Moderate	1.51 (0.71 to 3.24)	77.08	27.05	45.57
Severe	6.21 (3.28 to 11.77)	60.94	24.92	39.28
Intellectual impairment				
None	1.00	81.27	27.42	46.96
Mild–moderate	1.11 (0.62 to 1.97)	80.23	27.33	46.63
Severe–profound	3.01 (1.74 to 5.22)	69.59	26.21	42.84

I.3.4 Cost and healthcare resource use identification, measurement and valuation

The cost year for our analysis is 2018/19, as this is the most recent period for which national costs and inflators are currently available.

Where possible, we drew resource-use information from the primary evidence-base identified in our systematic review of clinical evidence (see 1.1.4 Effectiveness evidence). In the absence of such data, we attempted to locate published economic evaluations or costing studies providing relevant information. We filled any remaining gaps with estimates from the experts on the guideline committee.

We obtained unit costs for each of the resource-use elements from a number of standard sources.

- For drugs prescribed in secondary care, we use prices from the NHS Commercial Medicines Unit's Electronic Market Information Tool (eMIT; March 2020), where available. Otherwise, we use the NHS Prescription Services' Drug Tariff (July 2020).
- We use NHS Reference Costs 2016/17 as the source of unit costs for inpatient and outpatient procedures as well as hospital stay information. Although more recent schedules are available (2017/18 and 2018/19), neither contains any information on variability of costs (which is critical for our probabilistic model) and the latest figures do not include excess bad-days (which biases unit costs for any inpatient stays). Therefore, we concluded it was best to use the most recent schedule containing the data we need and inflate the relevant estimates to reflect 2018/19 values.
- We use the annual report on Unit Costs for Health and Social Care by the Personal Social Services Research Unit (PSSRU; 2019) to specify costs for both community and hospital-based healthcare staff.
- Where we cannot source an appropriate unit cost from these sources, we may use values from a relevant published study, in which case we inflate them to current prices using HCIS/NHSCII inflation indices from Unit Costs for Health and Social Care (PSSRU; 2019).

I.3.4.1 Drug costs

Table HE010 shows the unit costs we use to calculate drug costs.

Table HE010: Unit costs for drugs

	Cost (SD)	Quantity	Source / derivation
Fluconazole			
Fluconazole 200mg/100ml solution for infusion / Packsize 1	£1.21 (£1.81) (a)	97,804 (e)	eMIT March 2020
Fluconazole 200mg/100ml solution for infusion / Packsize 10	£6.75 (£23.89) (b)	3,223 (f)	eMIT March 2020
Fluconazole 200mg/100ml solution for infusion / Packsize 20	£18.81 (£113.78) (c)	1,044 (g)	eMIT March 2020
Fluconazole 50mg/25ml solution for infusion / Packsize 1	£8.88 (£3.34) (d)	13,694 (h)	eMIT March 2020
Fluconazole activity weighted average			
Fluconazole solution for infusion	£1.71	-	$\frac{ae + bf + cg + dh}{e + 10f + 20g + h}$
Fluconazole optimal acquisition price			
Fluconazole 200mg/100ml solution for infusion	£0.68	-	$\frac{b}{10}$
Nystatin			
Nystatin 100,000 units/ml oral suspension / Quantity 30 ml	£3.32	-	NHS Drug Tariff July 2020

As multiple purchasing options for fluconazole are available, we extracted the volume of each option from eMIT and calculated an activity-weighted average that we use as the price per vial of fluconazole in the base case of the model. Table HE010 shows the final cost and its derivation. Additionally, we calculated the cost of fluconazole assuming it is purchased at the current optimal acquisition price, that is to say, if only Fluconazole 200mg/100ml solution for infusion in a packsize of 10 were purchased. The optimal acquisition price of fluconazole per vial is only used in scenario analyses for two reasons: 1) Given the quantity of other fluconazole options being purchased, fluconazole is not only being purchased at its current optimal price 2) Even if fluconazole was only purchased at this optimal price, it is unknown if the price at which it is listed here would remain – it is very likely that if everyone only purchased a packsize of 10 the costs of this option would increase.

We calculated the total number of fluconazole infusions for the individual RCTs and derived an average number of infusions (weighted according to number of participants). Table HE011 shows the number of infusions given in the RCTs and the weighted average. Though the dose of fluconazole is dependent on the weight of the baby, for costing purposes, weight is irrelevant. This is because each vial contains 200 mg of fluconazole, which is substantially more than even the largest neonate receiving the highest dose would require. Therefore, neonates of any weight receiving prophylaxis will only require a small portion of the fluconazole solution for infusion and the rest will be wasted. Hence, we only need to know the number of infusions to calculate a cost.

Table HE011: Total number of fluconazole infusions given in RCT evidence

	N	Total number of infusions
RCT evidence		
Kicklighter 2001	53	24
Kirpal 2015	38	25
Parikh 2007	60	24
Aydemir 2011a	93	12
Benjamin 2014	188	12
Jannatdoust	43	26
Kaufman 2001	50	26
Manzoni 2007a	216	15.2
Mersal 2013	35	21
Violaris 2010	38	28
Kaufman 2005 (arm A: Infusions every 3 days for two weeks, every 2 days for two weeks, and every day for 2 weeks)	41	26
Kaufman 2005 (arm B: Infusions twice weekly)	40	12
Weighted average		
Weighted average number of infusions	-	**17.96**

We calculated the cost of fluconazole used in the model by multiplying the activity-weighted average for 1 vial of fluconazole by the weighted average number of infusions given in the RCTs.

We calculated the cost of a course of nystatin similarly, by multiplying the total number of bottles needed by the cost of a bottle. We calculated the total number of bottles used by taking the weighted average total number of doses from the RCT evidence (Table HE012) and dividing by the total number of doses per vial. On the advice of the committee, we then rounded this value up to a whole number to assume complete wastage of the final bottle. Table HE013 shows the costs used in the base case of the model as well as alternative values used in scenario analyses and their derivations.

Table HE012: Total number of nystatin treatments given in RCT evidence

	N	Treatments per day	Days of treatment	Total number of treatments
RCT evidence				
Aydemir 2011a	94	3	30	90
Ozturk 2006	475	3	(a)	-
Sims 1988	33	3	37 (b)	111
Mersal 2013	24	3	42	126
Violaris 2010	42	4	32.7	130.8
Rundjan 2020	47	3	42	126
Weighted average				
Weighted average total number of treatments	-	-	-	**110.7**

(a) Ozturk 2006 does not report a treatment duration in their study. As such, it was not possible to calculate a total number of treatments and this study was excluded from the weighted average calculation.

(b) Sims 1988 does not directly report a treatment duration. The study states treatment lasts for 1 week after endotracheal extubation. It also reports a mean of 30 days on a ventilator in the nystatin group. Therefore, we estimated the treatment duration to be 37 days.

Table HE013: Medication cost values used in the model

Drug	Treatment cost used for model	Derivation
Base Case		
Fluconazole	£30.70	£1.71 × 17.96
Nystatin	£13.28	£3.32 × 4 (a)
Alternative values		
Fluconazole	£12.12	£0.68 × 17.96
Nystatin	£12.25	£0.11 × 110.7 (b)

(a) Weighted averaged total number of treatments (110.7) divided by the number of doses in one bottle of nystatin (30) equates to 3.69 bottles of nystatin. Rounded up to 4 to assume complete wastage of the final bottle.

(b) Cost per dose (Total cost of vial divided by number of doses in one bottle) multiplied by the weighted average number of treatments calculated (110.7)

I.3.432 Costs associated with events

Cost associated with fungal infection

We expect that the costs associated with hospital care for the newborn baby will be substantially affected by the incidence of fungal infections. The committee reviewed evidence on length of hospital stay associated with candidiasis from a US study as no suitable UK studies were identified (Zaoutis et al. 2007). This study found, among extremely-low-birthweight infants, candidiasis was not associated with an increased length of hospital stay but was associated with increased total costs. Conversely, candidiasis in infants weighing over 1000 g was associated with an increased length of hospital stay of 16 days and substantially increased costs.

Similarly, one of the included RCTs in the systematic review (Sims et al. 1988) suggested that fungal colonisation did not increase overall length of stay in very-low-birthweight infants, but substantially increased the proportion of the stay during which babies required ventilation and/or indwelling lines.

These studies provide a broad, general indication that fungal infection increases neonatal care requirements and costs (though it is not certain that overall length of stay will be increased among the most premature babies). However, they cannot be relied on for model inputs, as they reflect US practice (in the case of Sims et al., from more than 3 decades ago).

Therefore, in the absence of specific evidence, the committee agreed to extrapolate from UK evidence on the impact of bacterial infections. In this area, a potentially valuable source of information is Schroeder et al.'s paper on the economic costs of group B streptococcus infection (2009), which we used to estimate costs of infection in our analysis of preterm prelabour rupture of membranes (see evidence review C). This study provides detailed information on resource use and total costs observed in cases of GBS compared with matched non-GBS controls. The committee agreed that late-onset GBS infection data from Schroeder et al. (2009) could serve as a proxy for invasive candidiasis. This paper presents data for early-onset GBS as well, but the committee expressed the view the data for late-onset GBS were more appropriate. This is because the population for our decision problem are suspected of late-onset (bacterial) infection, and early-onset GBS infection characteristically occurs in less premature, more robust newborns. In line with the committee's expectations, babies with late-onset GBS in this paper had a lower gestational age than those with early-onset disease.

There are 2 ways to use the data presented in Schroeder et al. (2009). One approach is to take the difference in total hospital care costs between late-onset GBS cases and non-GBS controls. The difference between these values is then inflated from 2003 (the cost year of the study) to 2018/2019. The other approach is to extract resource-use estimates for babies with late-onset GBS and babies without infection and value these using contemporary unit costs ('micro-costing'). Schroeder et al. do not explicitly present resource-use data for the late-onset GBS group; however, they do present costs in each category and the unit costs used to calculate them, so resource-use values can be inferred by dividing the former by the latter.

With both approaches, we rely on the difference between late-onset GBS cases and controls without infection to estimate the increase in resource-use associated with infection. Unfortunately, Schroeder et al. (2009) only present resource-use for the whole control group, rather than those that were matched with the babies with late-onset GBS, which would be an ideal group for comparison. This is likely somewhat to exaggerate the difference attributable to late-onset infection, as the control group will include less premature infants selected as controls for early-onset GBS cases. Nevertheless, the committee agreed that this as good an estimate as is available of the likely impact of costs associated with fungal infections.

Table HE014 shows the daily costs we use for the micro-costing calculations.

Table HE014: Unit costs (per day) for neonatal care

Level of care	Code	Submissions	Days	Mean cost per day (SE[a])[b]	Inflated to 2018/19
NICU	XA01Z[c]	129	159,664	£1,295 (£34)	£1,340
HDU	XA02Z[d]	129	183,555	£897 (£18)	£929
SCU	XA03Z[e]	129	535,683	£577 (£15)	£597
	XA04Z[f]	106	152,758	£418 (£19)	£432
	Weighted average			£542	£561
Postnatal ward	XA05Z[g]	96	61,167	£423 (£19)	£438

(a) Estimated from published interquartile range and number of submissions: SE = ([UQ−LQ] ÷ 1.349) ÷ √n, where 1.349 is 2 × the 0.75th quantile of the standard normal distribution.
(b) Cost year = 2016/17
(c) Neonatal Critical Care, Intensive Care
(d) Neonatal Critical Care, High Dependency
(e) Neonatal Critical Care, Special Care, without External Carer
(f) Neonatal Critical Care, Special Care, with External Carer
(g) Neonatal Critical Care, Normal Care

Table HE015 sets out the calculations for estimating the excess resource-use and costs associated with neonatal infections.

Table HE015: Cost calculations for fungal infections

Outcome	Days – mean (SE) (from Schroeder et al. 2009)				Total costs	Inflated to 2018/19
	NICU	HDU	SCU	Postnatal		
Base case – microcosting						
LOGBS	9.7 (3.2)	9.2 (2.2)	12.8 (3.0)	1.3 (1.1)	£28.348[a]	£29,339
Controls	1.9 (0.5)	1.4 (0.3)	4.6 (0.6)	2.0 (0.1)	£7,054[a]	£7,301
Difference	7.8 (3.3)	7.8 (2.2)	8.2 (3.0)	−0.7 (1.1)	£21,294[a]	£22,039
Scenario analysis – total costs from Schroeder et al. (2009)						
Difference	–	–	–	–	£13,315.70 (£3,288[b])[c]	£18,587

(a) Cost year = 2016/17
(b) Calculated from the difference between published total hospital care for LOGBS and Non-GBS controls
(c) Cost year = 2003

Cost associated with disability due to infection

As detailed in I.3.3.2, we account for lifelong neurodevelopmental morbidity secondary to neonatal fungal infection. The model subdivides cases into mild, moderate and severe impairment.

To estimate the costs with which these outcomes are associated, we rely on publications from the EPICure longitudinal study of premature babies in the UK and Ireland (Mangham et al. 2009, Petrou et al. 2013). The clear strength of these sources is that they provide detailed, UK-specific data on NHS, PSS and wider public sector costs associated with neurodevelopmental disability in a cohort followed up for over a decade, with contemporaneous controls. This is also the study we use to estimate the spectrum of severity of neurodevelopmental sequelae (see 0). This evidence has been used to quantify the impact of neonatal insults in several economic evaluations, including previous NICE

guidance (Specialist neonatal respiratory care for babies born preterm [NG124]) and published studies pertaining to neonatal infection (Grosso et al., 2019).

Alongside inflating the reported costs to present-day values, we also had to perform some calculations to estimate NHS+PSS costs and those associated with 'broader public sector' activity (this includes the costs of state-funded education). We do this by estimating a ratio between the 2 categories and applying it in all cases; this approach is similar to that adopted in NG124. In one of the publications (Petrou et al. 2013), the authors note that severe neurodevelopmental impairment resulted in an average unadjusted increase of £1,085 in NHS+PSS costs, and £8,797 in public sector costs. Although the authors do not provide a similar breakdown across all categories of impairment (or give an estimate of values adjusted for other clinical and sociodemographic factors, as they helpfully do for their total costs), we assume that the same ratio between NHS+PSS and other public sector costs applies throughout – that is, 1:8.1; equivalent to saying that NHS+PSS costs make up 11% of additional public expenditure, with other public sector costs (education) accounting for the remainder. Table HE016 provides details.

Table HE016: Annual costs associated with neurodevelopmental impairment

Category	Degree of neurodevelopmental disability			
	None	Mild	Moderate	Severe
Preschool (source: Mangham et al. 2009)				
Total absolute costs	£315.00[a]	£611.00[a]	£660.00[a]	£1,206.00[a]
Additional total costs of disability	–	£296.00	£345.00	£891.00
Inflated from 2005/06 to 2018/19	**–**	**£385.57**	**£449.39**	**£1,160.61**
Additional NHS+PSS costs of disability	–	£296.00[b]	£345.00[b]	£891.00[b]
Inflated from 2005/06 to 2018/19	–	£385.57	£449.39	£1,160.61
Additional public sector costs of disability	–	–[b]	–[b]	–[b]
Primary school (source: Mangham et al. 2009)				
Total absolute costs	£3,467.00[a]	£3,763.00[a]	£4,814.00[a]	£12,389.00[a]
Additional total costs of disability	–	£296.00	£1,347.00	£8,922.00
Inflated from 2005/06 to 2018/19	**–**	**£385.57**	**£1,754.59**	**£11,621.73**
Additional NHS+PSS costs of disability	–	£32.50[c,d]	£147.89[c,d]	£979.60[c,d]
Inflated from 2005/06 to 2018/19	–	£42.33	£192.65	£1,276.01
Additional public sector costs of disability	–	£263.50[c,d]	£1,199.11[c,d]	£7,942.40[c,d]
Age 11 onwards (source: Petrou et al. 2013)				
Total absolute costs	NR	NR	NR	NR
Additional total costs of disability	–	£3,612.17[e]	£5,969.27[e]	£9,701.66[e]
Inflated from 2006/07 to 2018/19	**–**	**£4,537.54**	**£7,498.50**	**£12,187.07**
Additional NHS+PSS costs of disability	–	£396.60[a,f]	£655.40[a,f]	£1,065.20[a,f]
Inflated from 2006/07 to 2018/19	–	£498.20	£823.30	£1,338.09
Additional public sector costs of disability	–	£3,215.57[c,g]	£5,313.87[c,g]	£8,636.46[c,g]

(a) These are the data directly reported in the publications
(b) Although it is not entirely clear, it appears that the authors only include education in the category of 'broader public sector' costs; therefore, we assume that 100% of total costs for preschool children relate to NHS+PSS expenditure
(c) We assume that the ratio between NHS+PSS and other public sector costs is 1:8.11 (based on information in Petrou et al. 2013; see text)

Category	Degree of neurodevelopmental disability			
	None	Mild	Moderate	Severe

(d) We use the assumed ratio to estimate the split between NHS+PSS and other public sector costs, from the published total amount for the 2 categories
(e) Sum of published NHS+PSS costs and estimated additional public sector costs
(f) Estimates from a multivariable model adjusting for various clinical and sociodemographic factors, in an attempt to isolate the independent impact of neurodevelopmental impairment
(g) We use the assumed ratio to estimate additional public sector costs, from the published NHS+PSS costs

Previous economic evaluations simulating the consequences of neonatal infection (Colbourn et al. 2007, CG149) have used long-term cost estimates that can be traced to a model of meningitis vaccination published by Trotter and Edmunds (2002). Those authors assumed 10% of meningitis survivors would require lifelong, full-time residential care and the remainder would accrue additional healthcare costs £500 per year, though no empirical basis is provided. While we are confident that our base-case costing represents a more evidence-based method, we replicate the older approach in a sensitivity analysis, to see if the methods adopted by earlier modellers have a meaningful effect on results. The equivalent numbers are £79,013.93 per year for severe impairment (derived from the Adult Social Care Activity and Finance Report, England – 2018–19) and £831.90 per year for mild and moderate disability (£500 inflated from 1999/2000 to 2018/19).

Costs incurred by carers (including lost productivity)

Some published cost–utility analyses in related areas have adopted a broad societal perspective, including accounting for costs incurred by carers of neonates with long-term morbidity, which may also include their lost earnings. However, Developing NICE guidelines stipulates that such costs should not be included in the economic analyses considered by NICE's decision-making committees.

I.3.5 Quality of life

The model estimates QALYs for babies. These QALYs are presented as total lifetime QALYs, as some of the events modelled may have effects on life expectation and lifelong impairment.

Evidence shows that using the baseline utility of perfect health (utility=1) ignores the natural decline in mental/physical functions due to age and co-morbidities which also affect QoL. This also assumes the detriment on QoL associated with a health condition is constant irrespective of age (Ara and Brazier, 2010). To avoid these limitations, the baseline utility that was applied in the economic model is based on age-adjusted EQ-5D data for UK general population (Kind, Hardman and Macran, 1999).

I.3.5.1 Utility associated with neonatal events

The model does not account for QALY loss for the neonate due to the initial acute events, as the duration of these events is relatively short and there is no way of empirically quantifying HRQoL in affected neonates.

However, the committee emphasised that, when a newborn baby needs critical care, it is invariably an extremely stressful experience for the parents. Therefore, any mode of management that can increase or reduce the duration of NICU admission is likely to have an impact on the QoL. We found no published information relating to the quality of life of parents of babies on NICU. Therefore, we have included an approximate estimate of the maternal

impact of neonatal intensive care. We assume that the mother of a child in intensive care will be extremely anxious. We note that the EQ-5D utility value for an otherwise healthy person with extreme anxiety or depression is 0.414, which is 0.516 lower than the average for woman in the UK aged 25–34. This would give an annualised QALY decrement of 0.516, which equates to a loss of 0.001413 QALYs per day. The model therefore assumes that each day in NICU is associated with this level of QALY loss. As this figure lacks empirical foundation, we fitted a broad triangular distribution to vary this parameter in probabilistic analyses and tested the impact in deterministic sensitivity analysis.

For our estimate of the length of critical care days (critical care here to mean NICU, HDU and SCU days) we again rely on data from Schroeder et al. (2009), as previously detailed in Table HE015. We multiply the predicted proportion of infants with candidiasis by the anticipated increase in critical care days associated with a case of candidiasis estimated using Schroeder et al.'s data as a proxy measure (7.8 days' NICU + 7.8 days' HDU + 8.2 days' SCU = 23.9 days; see in I.3.4.2, below). We then multiply this by the QALY decrement per critical care day to estimate the additional QALYs lost for increased NICU duration as a result of candidiasis.

Table HE017 sets out the calculations for our approach.

Table HE017: QALY-loss calculations for NICU

Strategy	Proportion with invasive candidiasis	Average increase in critical care days[a]	Difference compared with no prophylaxis	Difference in QALYs lost
Base-case approach at indicative gestational age[b]				
No prophylaxis	3.14%	0.749	–	–
Fluconazole	0.81%	0.194	−0.555	−0.0008
Nystatin	0.52%	0.125	−0.624	−0.0009

(a) Proportion with candidiasis × 23.9 (average increase in critical care days ascribable to candidiasis)

(b) 24.83 weeks' gestation without exposure to broad-spectrum antibiotics – chosen because this gives an expected rate of invasive candidiasis without prophylaxis of 3.14%, as observed in the study we have used for base-case absolute risk (Oeser et al. 2014; see I.3.2.3).

The model also does not account for QALY loss to the family in the event of neonatal death. A recent analysis by NICE's Decision Support Unit (DSU; Pennington and Wong 2019) examining how health-related quality of life has been modelled for carers found only 1 relevant analysis. This was a model submitted by the manufacturer of a technology undergoing highly specialised technology assessment that included a QALY loss seeking to quantify the impact of a child's death (NICE HST7). However, this impact was not included in the company's base case: it was a scenario analysis achieved by synthesising heterogeneous pieces of evidence that were of tenuous relevance to the decision problem. Accordingly, NICE's decision-making committee considered the analysis did not accurately quantify the impact, and chose to consider this aspect of their decision problem in qualitative terms. Aside from this model, the DSU analysis found relatively little evidence from the wider literature on estimating the QALY impact on carers, and none regarding a QALY loss to the family in the event of child death (Pennington and Wong 2019).

Therefore, in the absence of a credible way to quantify the impact, our model does not estimate the QALY loss to the family in the event of neonatal death. We acknowledge that this is a limitation of the model. Further research is needed to accurately estimate the impacts on the family in instances of events such as neonatal death.

I.3.512 Utility associated with long-term disability due to invasive candidiasis

Previous analyses (including Colbourn et al. 2007 and CG149) have accounted for long-term neurological impairment secondary to neonatal infection using utility estimates from Oostenbrink et al. (2002). This study used the EQ-5D to estimate HRQoL associated with permanent sequelae of meningitis. However, the valuations of each outcome were given by Dutch clinicians (rather than patients or carers, as NICE's methods prefer) and do not explicitly relate to the outcomes modelled – for mild disability, previous authors have used Oostenbrink et al.'s value for deafness as a proxy; for moderate disability, they have relied on the category 'mild mental retardation'; for severe disability, 'epilepsy, mental retardation and leg paresis'. These factors make this source suboptimal, so we reserve it for a scenario analysis.

Instead, our base-case relies on values from a more recent UK cohort of extremely preterm babies followed up until 11 years of age. The valuations are from the children's parents and are based on the Health Utilities Index Mark 3 (HUI3) instrument. As this study also includes a contemporaneous control group, we can calculate utility multipliers directly; see Table HE018. Despite our misgivings about the derivation of values from Oostenbrink et al.'s study, the multipliers for each category are relatively similar.

Table HE018: Utility associated with neurodevelopmental disability following meningitis or sepsis

	N	Utility / disutility by level of impairment			
		None	Mild	Moderate	Severe
Base case					
Petrou et al. (2013)	196	0.959 (SE 0.008)[a]	−0.179 (SE 0.042)[b]	−0.298 (SE 0.055)[b]	−0.558 (SE 0.084)[b]
			0.813[c]	0.689[c]	0.418[c]
Alternative value (scenario analysis)					
Oostenbrink et al. (2002)	28	1.000	0.810 (SD 0.150)[d]	0.620 (SD 0.110)[d]	0.470 (SD 0.250)[d]

(a) Control group (N=135) of mainstream school classmates
(b) Values are absolute disutilities compared with no impairment, estimated from multivariable regression adjusting for clinical and sociodemographic confounders
(c) Equivalent utility multipliers
(d) Published values are absolute utility estimates using EQ-5D; however, as they are the result of an exercise in which clinicians were asked to rate various sequelae alongside a 'healthy' state, they can be interpreted as relative to utility of 1; therefore, we can treat them as utility multipliers

I.4 Results

The model generates results for babies born at each gestational age from 22 weeks to 42 weeks. Altogether this produces 42 unique sets of results. Rather than present results for all these combinations, we display results with and without exposure to broad-spectrum antibiotics at 4 gestational ages (23, 28, 33 and 38 weeks). This approach shows sufficient details to illustrate the overarching trends of the model without reproducing outputs for all 42 analyses.

I.4.1 Base-case deterministic results

I.4.1.1 Incidence of candidiasis

As seen in Figure HE008, the rates of candidiasis predicted by the model are highest at low gestational ages; as gestational age increases, the rates of candidiasis observed in the model decrease. By 33 weeks' gestational age, the expected rates of candidiasis, regardless of prophylaxis strategy, are nearly zero. Additionally, Figure HE008 shows that antifungal prophylaxis with both nystatin and fluconazole results in lower observed rates of candidiasis, though nystatin is slightly more effective than fluconazole.

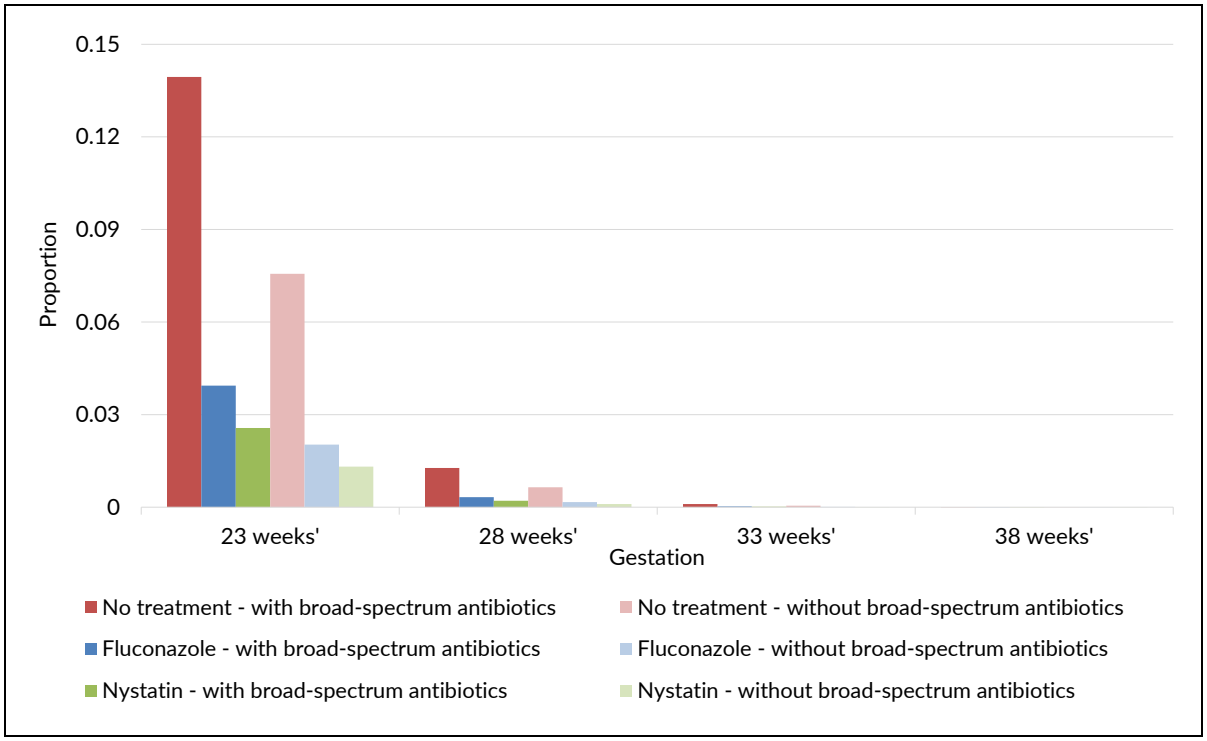


Figure HE008: Incidence of invasive candidiasis for each strategy at indicative gestational ages

I.4.1.2 QALYs

Figure HE009 depicts the QALY losses attributable to candidiasis (note the scale of the vertical axis changes in each gestational age so that the magnitude of each loss is visible on each graph) . At low gestational ages, the largest QALY loss occurs as a result of candida-related deaths. This occurs for two reasons: (1) The QALYs lost due to a single case of candidiasis-related death represent a larger loss compared with the QALYs lost in a single case of severe neurological impairment. (2) At lower gestational ages, observed mortality

due to candidiasis is higher. At 23 weeks, the model predicts that 75% of infants who develop candidiasis will die. Of those who survive, most will experience neurodevelopmental sequelae, but QALY losses for an average baby are dominated by the risk of death. However, as gestational age increases, the observed percentage of infants dying as a result of candidiasis decreases and, with more survivors, the percent of infants who survive with some level of NDI post-candidiasis increases. This results in fewer QALYs being lost due to candida-related death and an increasing number of QALYs being lost as a result of NDI-post candidiasis.

At lower gestational ages, the QALYs lost as a result of the duration of NICU stays while important, remain significantly smaller by comparison than the QALYs lost either due to candidiasis-related deaths or NDI-post candidiasis. It is only at the highest of gestational ages when one can even see the QALYs lost as a result of the duration of NICU stays. This visibility is only because at these gestational ages, the QALYs lost in any category, are so small that they scale used in the graphs allow for the QALY losses across all categories to be easily observed.

I.4.163 Costs

As illustrated in Figure HE010 (note the scale of the vertical axis changes in each gestational age so that the magnitude of costs fits on each graph), at lower gestational ages, the costs incurred as a result of infection and NDI are nearly equivalent. As for QALYs, at low gestational ages, the incidence of candidiasis is high, but so too is the predicted mortality rate. This results in significant costs associated with treating instances of candida infections but limits the long-term costs due to NDI post-candidiasis since most infants who develop candidiasis will not survive. As gestational age increases, costs incurred as a result of NDI post-candidiasis overtake costs incurred as a result of infection as the most significant costs predicted by the model. However, both costs due to infection and NDI post-candidiasis move towards zero as gestational age increases. This result stems from the fact that we expect to see fewer cases of candidiasis at a higher gestational age; therefore, the immediate costs of infection decrease as do costs associated with NDI. The cost of prophylaxis remains constant across gestational age. At a lower gestational age, the costs of prophylaxis are dwarfed by the costs of infection and NDI. However, at higher gestational ages, the costs of prophylaxis become increasingly important as the costs of infection and NDI decrease.

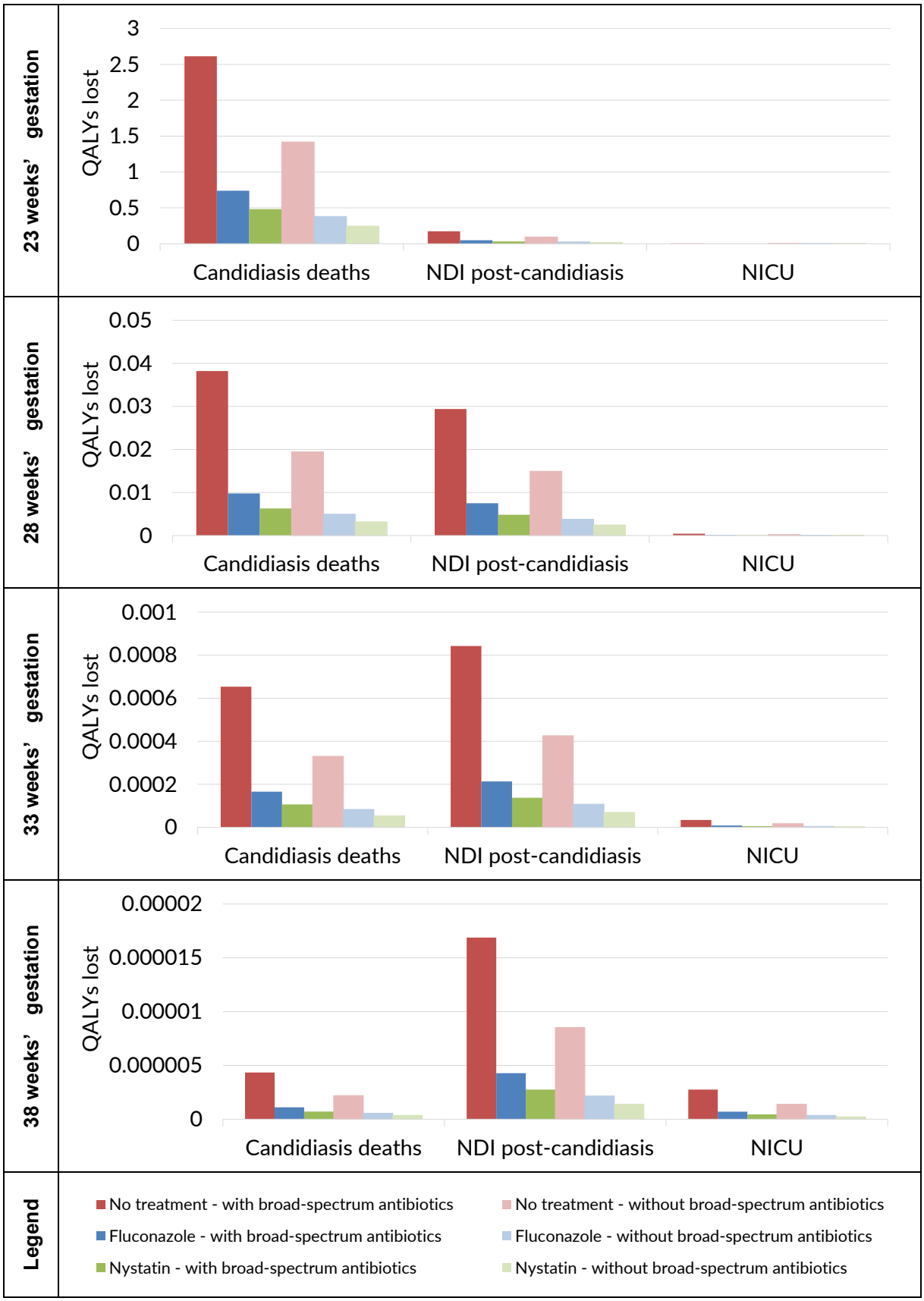


Figure HE009: Breakdown of QALYs lost for each strategy at indicative gestational ages

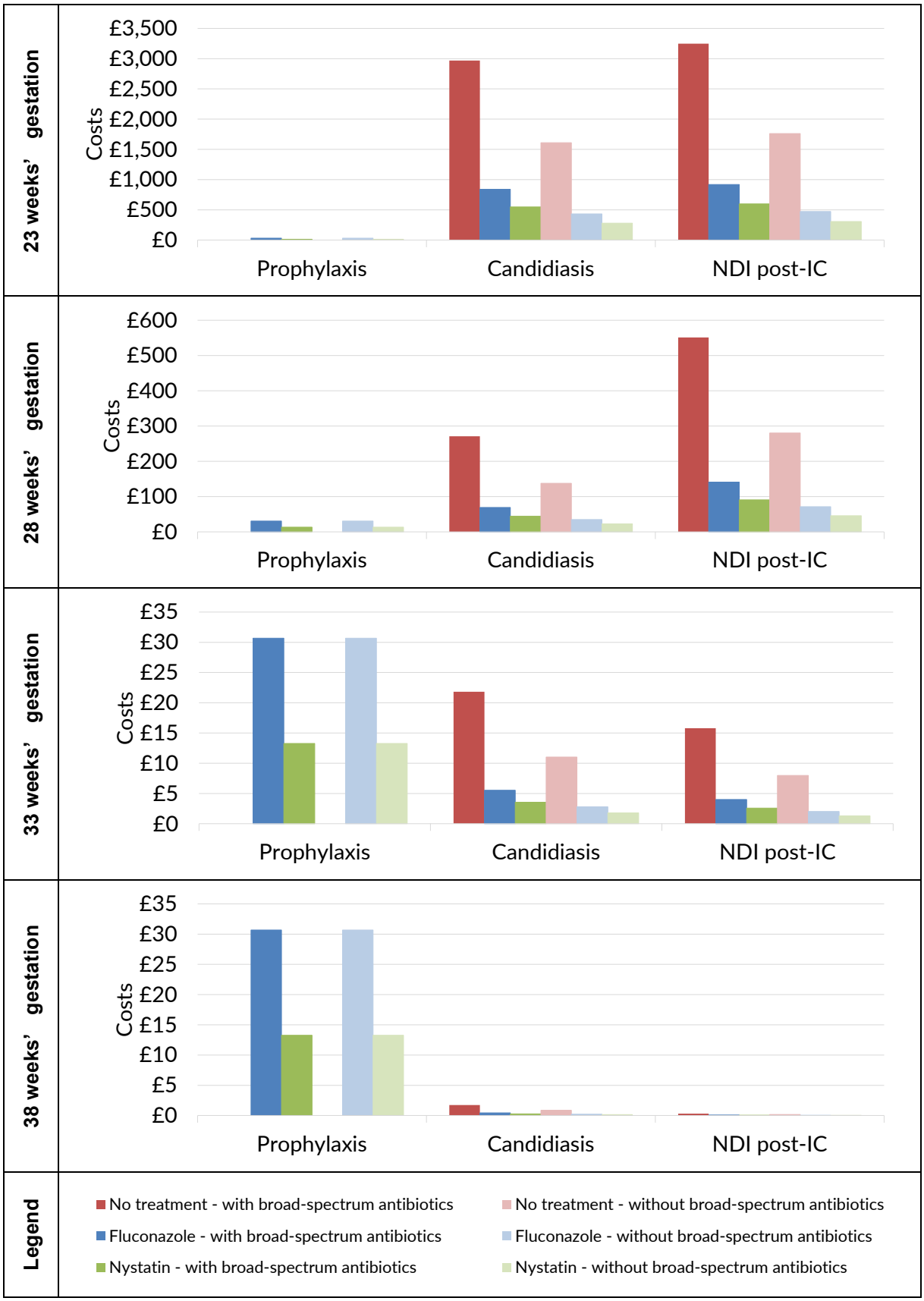


Figure HE010: Breakdown of costs for each strategy at indicative gestational ages

I.4.114 Cost–utility

Table HE019 shows base-case deterministic results. As detailed above, at lower gestational ages, nystatin is associated with both more QALYs and lower costs compared with both fluconazole and no prophylaxis. This is true regardless of whether a baby has been given broad-spectrum antibiotics. At 33 weeks' gestation, for babies without exposure to broad-spectrum antibiotics, nystatin no longer dominates no prophylaxis, but instead produces an ICER value of £1,264/QALY. At 34 weeks, however, this value increases beyond £20,000/QALY. There is a similar change in babies with exposure to broad-spectrum antibiotics; however, it occurs between 34 and 35 weeks' gestation. At 34 weeks nystatin remains dominant over no prophylaxis, but at 35 weeks it produces an ICER of £36,426.36/QALY. As gestational age continues to increase beyond 35 weeks, both with and without exposure to broad-spectrum antibiotics, the ICER for nystatin continues to increase. Figure HE011 plots these results on the cost–utility plane.

1 **Table HE019: Base-case deterministic cost–utility results**

Strategy	Absolute		Incremental			Net health benefit	
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/ QALY	£30K/ QALY
23 weeks' gestation							
Without broad-spectrum antibiotics							
Nystatin	£30,583	9.2995				7.7703	8.2801
Fluconazole	£30,702	9.2683	£119	-0.03120	dominated	7.7332	8.2449
No prophylaxis	£31,457	9.0272	£874	-0.27232	dominated	7.4543	7.9786
With broad-spectrum antibiotics							
Nystatin	£30,761	9.2448				7.7067	8.2194
Fluconazole	£30,974	9.1850	£212	-0.05980	dominated	7.6363	8.1525
No prophylaxis	£32,363	8.7492	£1,602	-0.49561	dominated	7.1310	7.6704
28 weeks' gestation							
Without broad-spectrum antibiotics							
Nystatin	£25,656	22.2610				20.9782	21.4058
Fluconazole	£25,696	22.2594	£40	-0.00156	dominated	20.9746	21.4029
No prophylaxis	£25,854	22.2467	£198	-0.01432	dominated	20.9540	21.3849
With broad-spectrum antibiotics							
Nystatin	£25,696	22.2582				20.9734	21.4017
Fluconazole	£25,759	22.2552	£63	-0.00307	dominated	20.9672	21.3965
No prophylaxis	£26,098	22.2301	£401	-0.02814	dominated	20.9252	21.3602
33 weeks' gestation							
Without broad-spectrum antibiotics							
No prophylaxis	£7,165	24.4007				24.0424	24.1618
Nystatin	£7,166	24.4011	£0	0.00037	£1,264	24.0428	24.1622
Fluconazole	£7,185	24.4010	£19	-0.00004	dominated	24.0418	24.1615
With broad-spectrum antibiotics							
Nystatin	£7,168	24.4010				24.0426	24.1620
No prophylaxis	£7,180	24.4003	£12	-0.00073	dominated	24.0412	24.1609
Fluconazole	£7,188	24.4009	£20	-0.00008	dominated	24.0415	24.1613
38 weeks' gestation							
Without broad-spectrum antibiotics							
No prophylaxis	£1,673	24.9623				24.8787	24.9066
Nystatin	£1,686	24.9623	£12	0.00001	£1,927,997	24.8781	24.9061
Fluconazole	£1,703	24.9623	£17	0.00000	dominated	24.8772	24.9056
With broad-spectrum antibiotics							
No prophylaxis	£1,674	24.9623				24.8786	24.9065
Nystatin	£1,686	24.9623	£12	0.00001	£911,752	24.8780	24.9061
Fluconazole	£1,703	24.9623	£18	0.00000	dominated	24.8772	24.9056

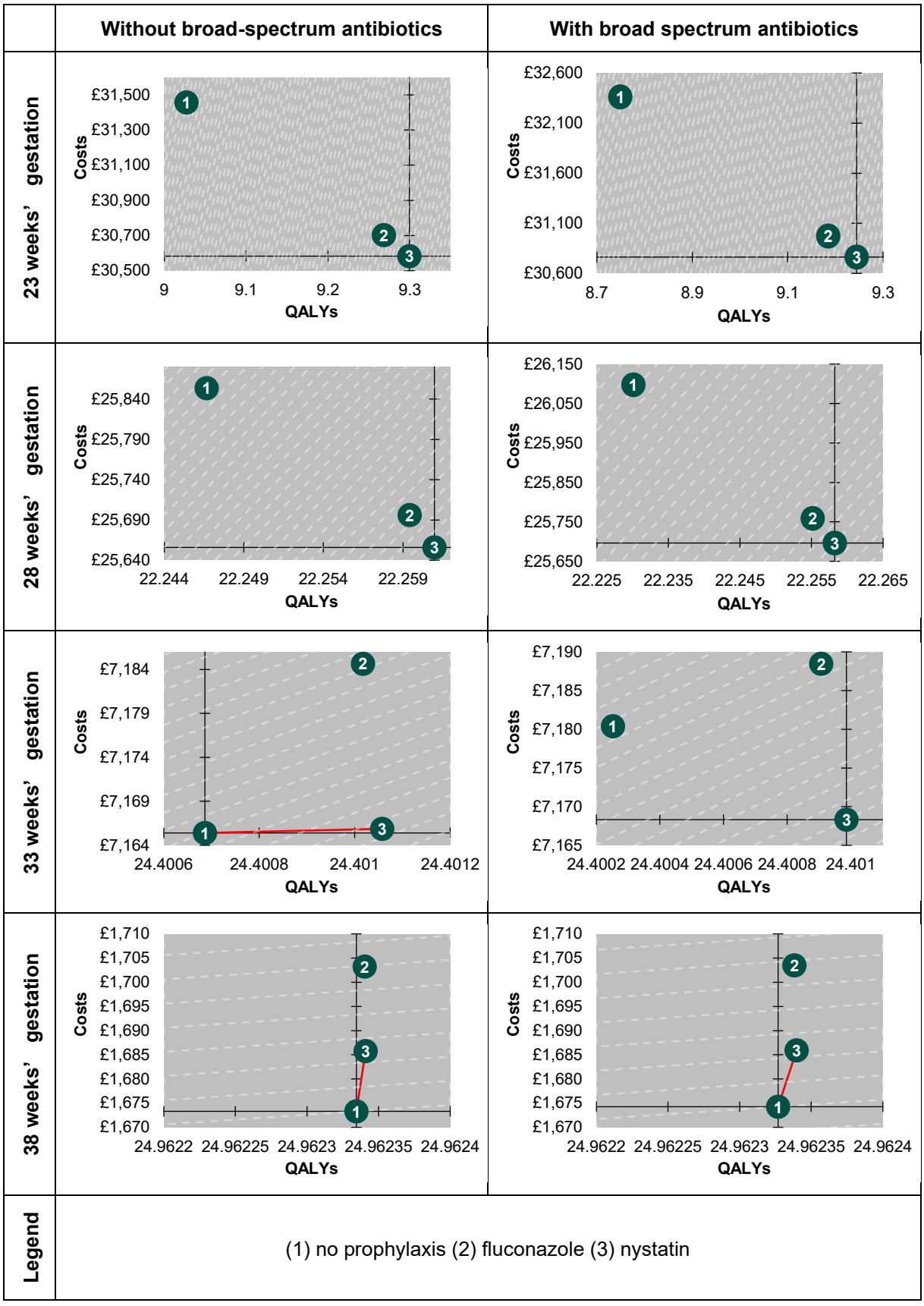


Figure HE011: Base-case deterministic cost–utility results at indicative gestational ages

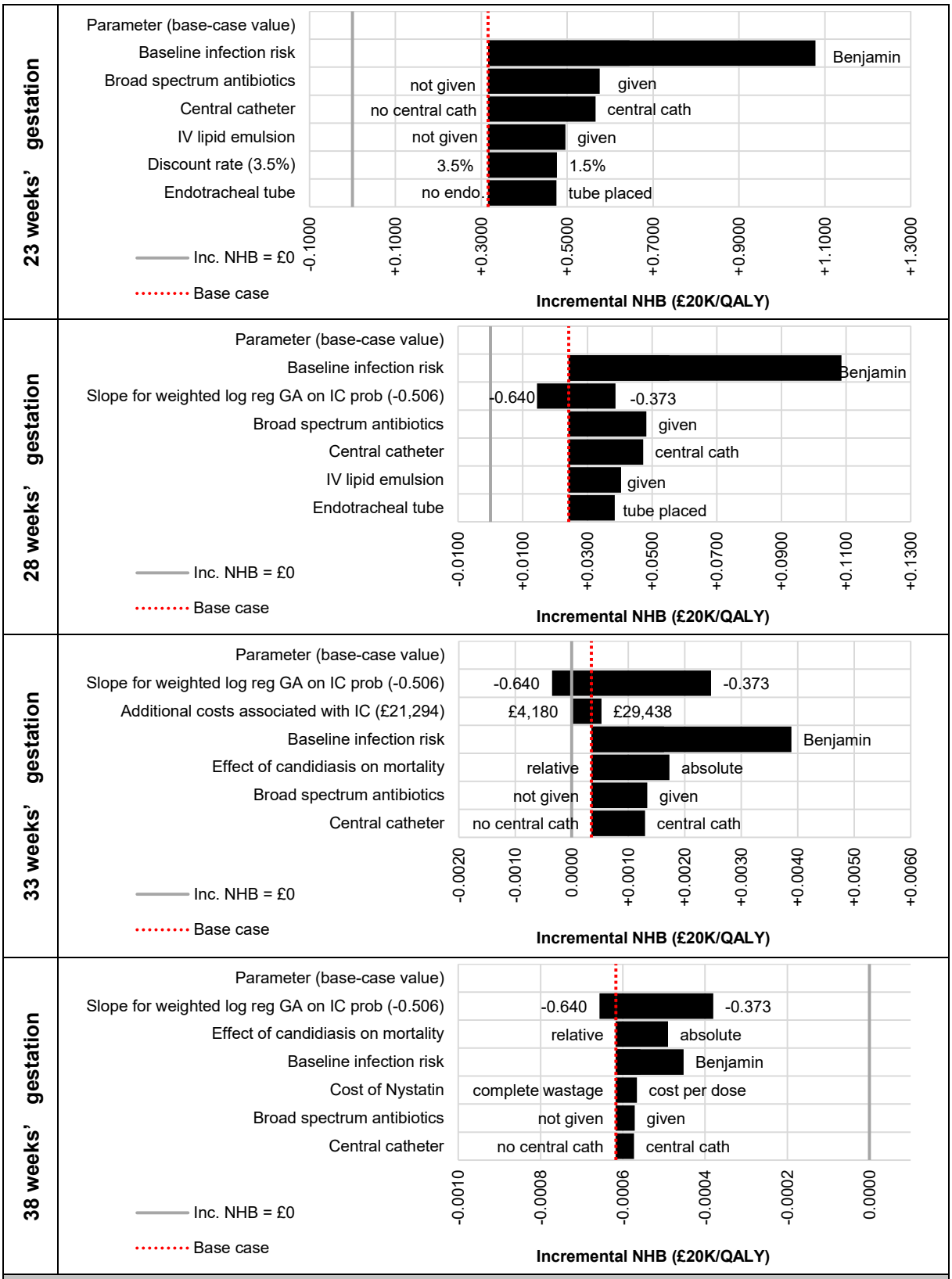
I.4.12 Sensitivity analysis

I.4.221 One-way sensitivity analysis

At a low gestational age, regardless of exposure to antibiotics, there is no single parameter that can be varied within the range of its confidence interval such that nystatin is not the optimal option when compared with no prophylaxis. Figure HE013 and Figure HE012 (note that while only the 6 most influential parameters are displayed here, all parameters for which a confidence interval existed were subject to one-way sensitivity analysis) illustrate this fact as the tornado diagrams for both 23 and 28 weeks' gestation regardless of antibiotic exposure always have a positive incremental net health benefit. This remains the case until 33 weeks' and 32 weeks' gestation for babies with and without exposure to broad-spectrum antibiotics, respectively. At these gestational ages, we begin to see parameters that can be varied such that nystatin is no longer the optimal option. By 38 weeks' and 37 weeks' gestation for babies with broad-spectrum antibiotic exposure and babies without broad-spectrum antibiotic exposure, respectively, there is no single parameter that can be varied within the range of its confidence interval such that no prophylaxis is not the optimal option.

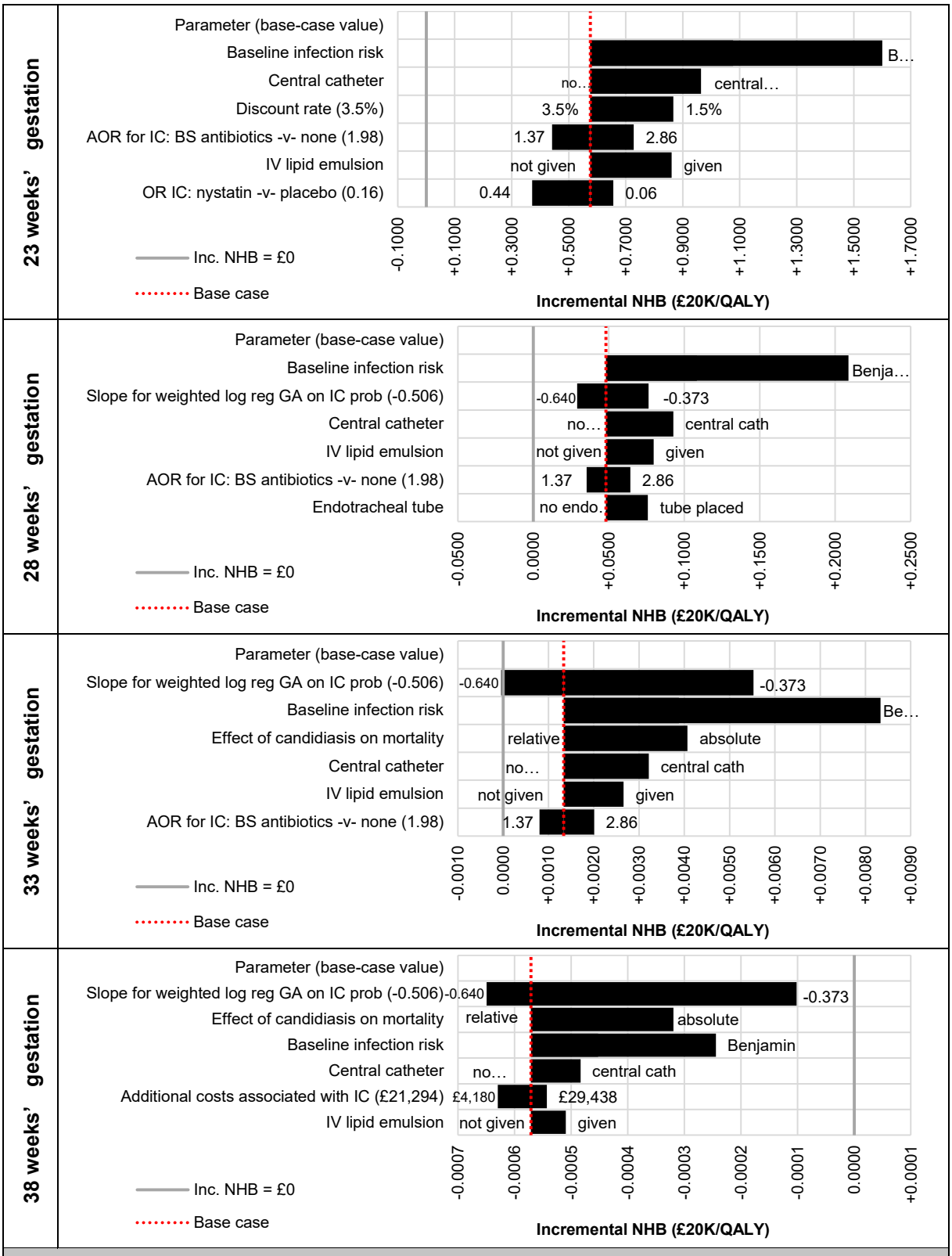
Because the costs of infection at lower gestational ages are so significant, the model is not sensitive to any one-way sensitivity analysis, and whichever treatment is best at preventing candidiasis is preferred. However, at higher gestational ages when the likelihood of infection is increasingly small, no single parameter can make no prophylaxis not optimal. This is because, while infections remain a severe negative consequence, at this point they become so rare that a positive incremental net benefit cannot be achieved as they are incredibly unlikely to occur.

Figure HE014 represents one-way sensitivity analysis at 28 weeks' gestation comparing nystatin with fluconazole. Regardless of exposure to antibiotics, the only parameters that the model is sensitive to are the odds ratio of infection versus placebo for nystatin, and the odds ratio of infection versus placebo for fluconazole. If fluconazole is better at preventing infection than in the base case of the model, or nystatin is worse at preventing infection than in the base case of the model, fluconazole would represent the better option.



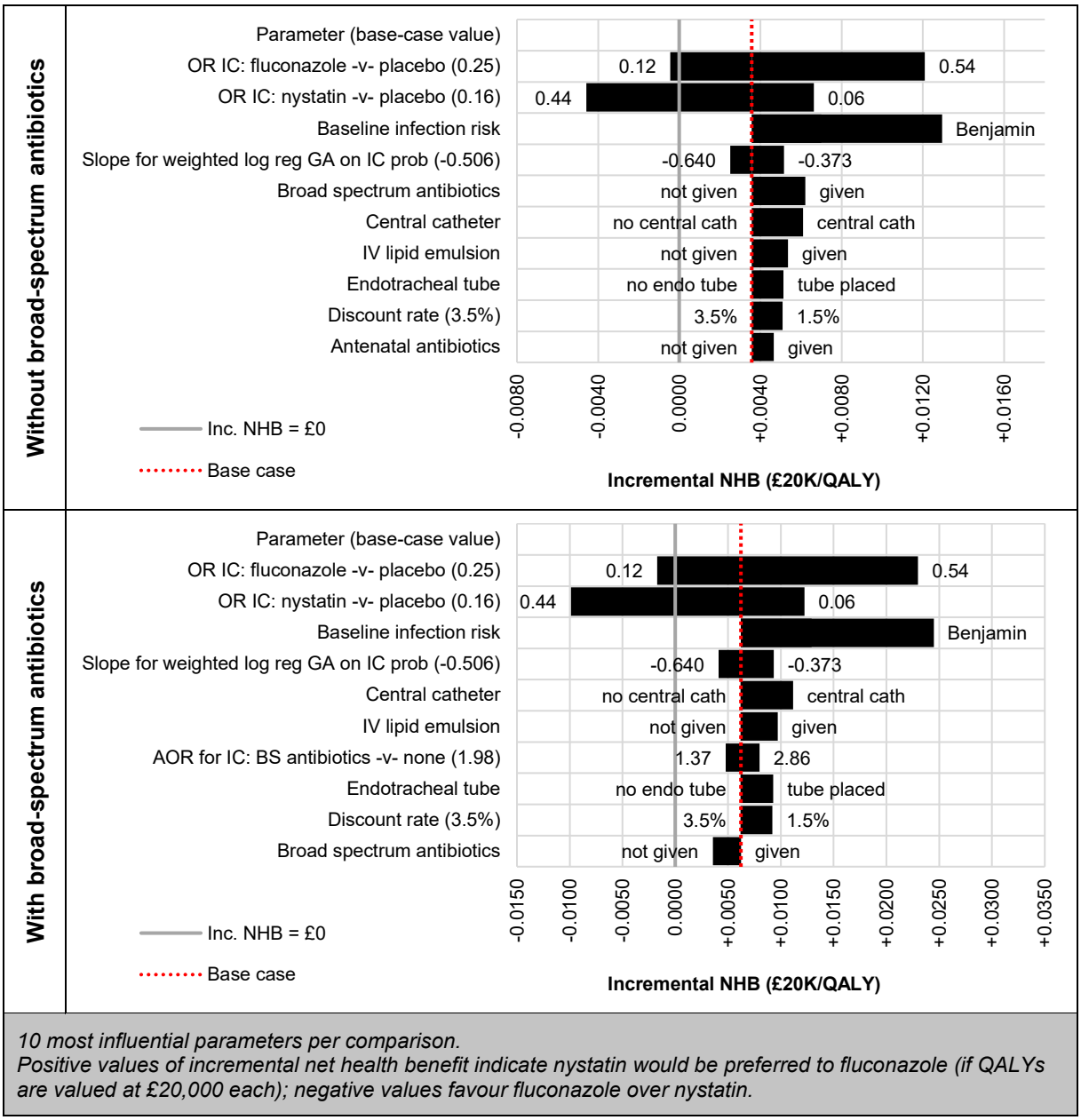
6 most influential parameters per comparison.
Positive values of incremental net health benefit indicate nystatin would be preferred to no prophylaxis (if QALYs are valued at £20,000 each); negative values favour fluconazole over nystatin.

Figure HE012: One-way sensitivity analysis – nystatin -v- no prophylaxis – at indicative gestational without broad-spectrum antibiotics



6 most influential parameters per comparison.
Positive values of incremental net health benefit indicate nystatin would be preferred to no prophylaxis (if QALYs are valued at £20,000 each); negative values favour fluconazole over nystatin.

Figure HE013: One-way sensitivity analysis – nystatin -v- no prophylaxis – at indicative gestational with broad-spectrum antibiotics

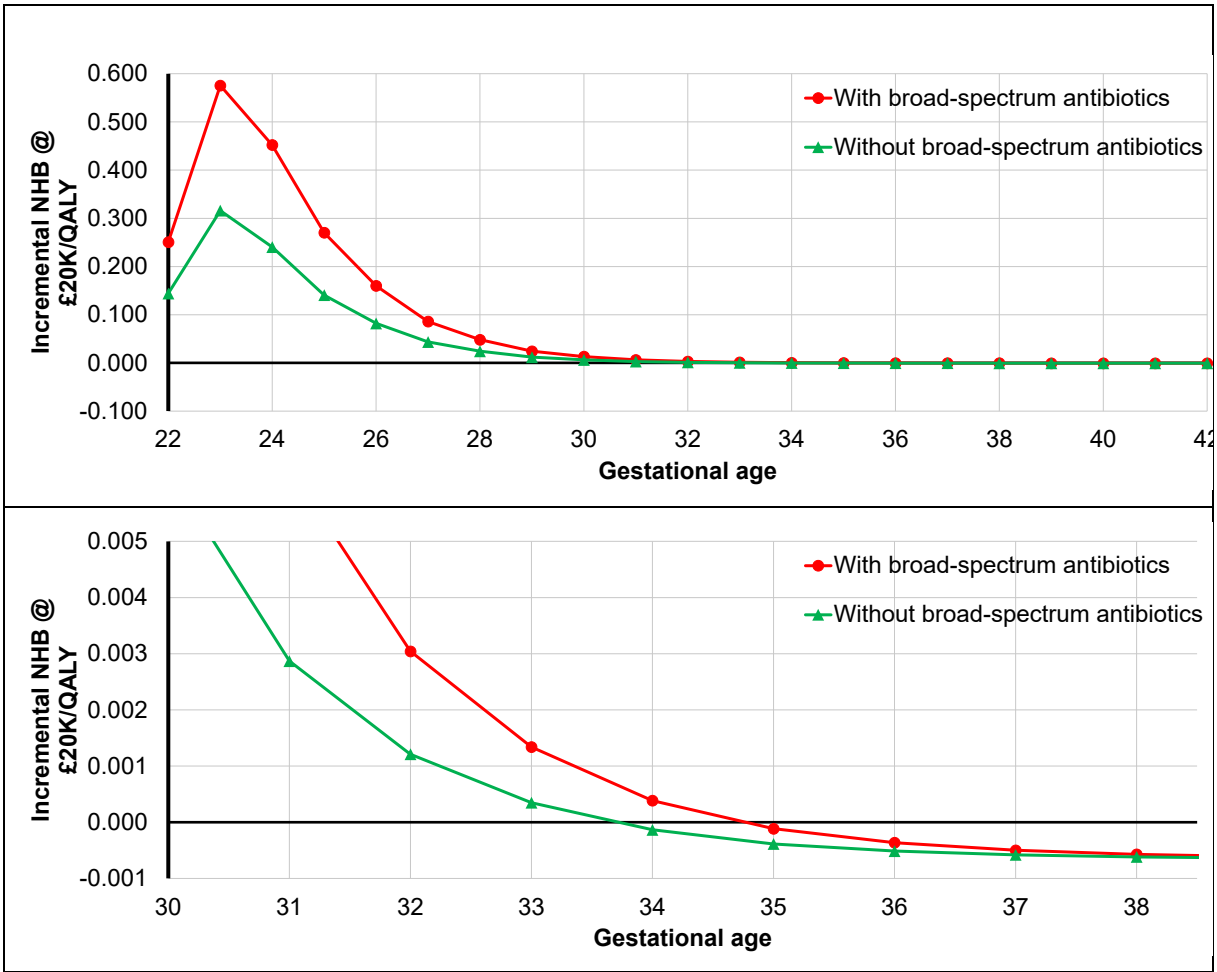


10 most influential parameters per comparison.
Positive values of incremental net health benefit indicate nystatin would be preferred to fluconazole (if QALYs are valued at £20,000 each); negative values favour fluconazole over nystatin.

Figure HE014: One-way sensitivity analysis – nystatin -v- fluconazole – at 28 weeks' gestation – tornado diagrams

We also performed a detailed one-way sensitivity analysis on gestational age (Figure HE015) and the odds ratio of infection for fluconazole -v- placebo (Figure HE016). Figure HE015 gives a visual overview of the relationship between gestational age and cost effectiveness that is detailed in base-case results, above. It shows that, at gestational ages up to 33 weeks, prophylaxis with nystatin is associated with positive incremental net health benefit – that is, it would be associated with an ICER of £20,000/QALY or better compared with no prophylaxis. Conversely, at gestational ages of 35 weeks and higher, nystatin is associated with negative incremental net health benefit – that is, an ICER worse than £20,000/QALY compared with no prophylaxis. It is only for neonates born at 34 weeks' gestation that model results are qualitatively influenced by exposure to broad-spectrum antibiotics. Where broad-spectrum antibiotics are used, nystatin remains the dominant strategy; where there is no

such exposure, neither nystatin nor fluconazole are good value for money (that is, they are both associated with ICERs worse than £20,000 per QALY).



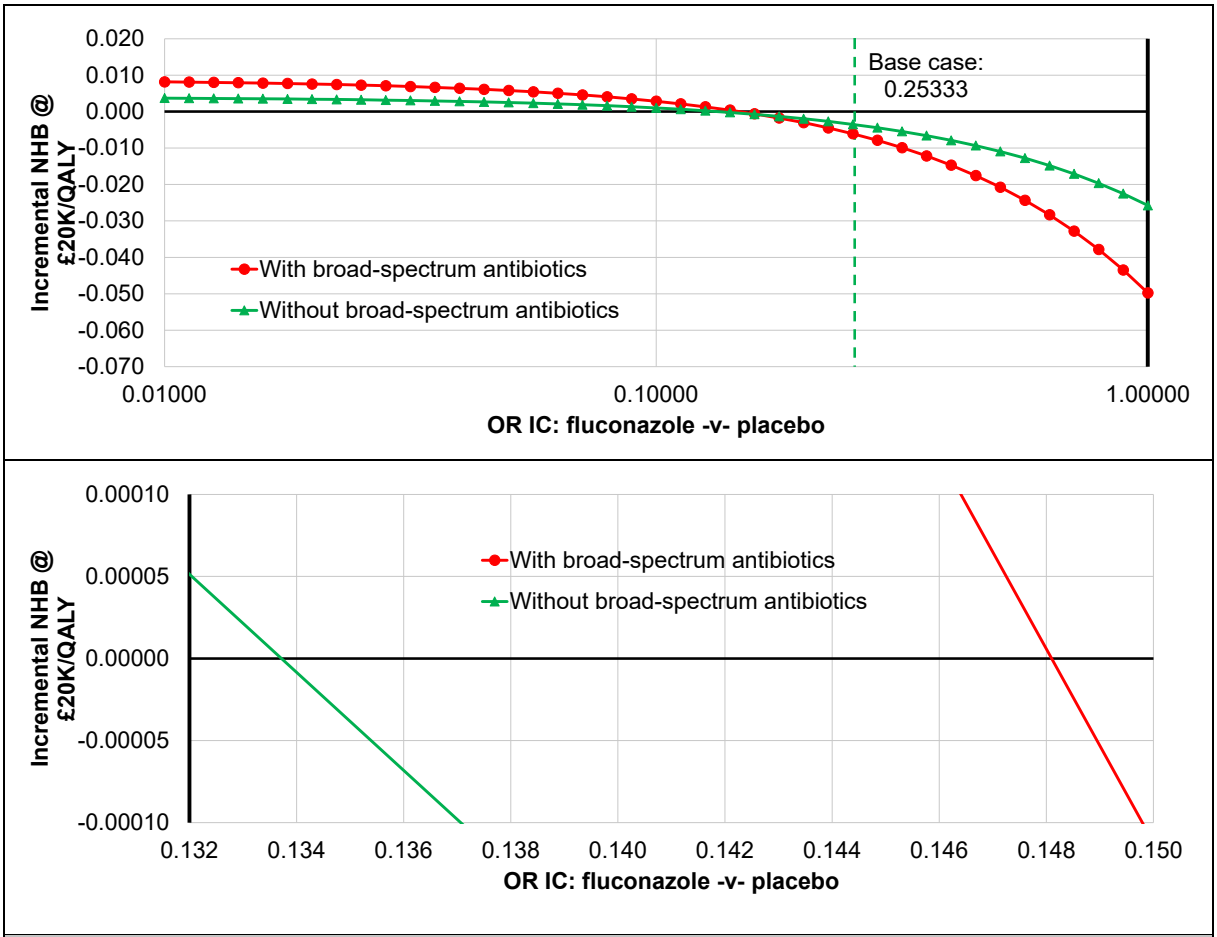
Lower panel shows detail from upper panel.
Incremental net health benefit of nystatin compared with no prophylaxis. Positive values indicate nystatin would be preferred (if QALYs are valued at £20,000 each); negative values favour no prophylaxis over nystatin.

Figure HE015: One-way sensitivity analysis – nystatin compared with no prophylaxis as a function of gestational age

Figure HE016 visually depicts the influence on model outputs of the odds ratio for fluconazole compared with placebo in preventing invasive fungal infections at 28 weeks' gestation, to establish how effective fluconazole would need to be in order to represent better value for money than nystatin. It shows that, if broad-spectrum antibiotics are used, any odds ratio lower than 0.148 would give fluconazole positive incremental net monetary benefit compared with nystatin – that is, it would have an ICER better than £20,000/QALY for that comparison. Without broad-spectrum antibiotics, the analogous figure is around 0.134. It makes sense to interpret these with reference the base-case odds ratio for nystatin versus placebo, which is 0.163 (this would be the exact point at which fluconazole would become favoured, in this analysis, if the 2 options' costs were identical).

Further analysis (not shown) indicates that, as gestational age decreases from 28 weeks, the odds ratio at which fluconazole would be preferred to nystatin moves towards 0.163. However, as gestational age increases from 28 weeks, the equivalent tipping point moves towards 0, with the last gestational age for which fluconazole can have a positive incremental

net monetary benefit being 31 weeks' gestation. At lower gestational ages, the costs of prophylaxis are insignificant when compared with the costs attributable to candidiasis. Thus, fluconazole only needs to be as effective as nystatin in order to represent good value for money. But, at higher gestational ages, the baseline risk of candidiasis is lower, which in turn leads to a reduction in costs associated with candidiasis. Ultimately, this leads to the costs of prophylaxis becoming more significant. As fluconazole is more expensive than nystatin, this additional cost becomes the crucial factor. Fluconazole could be 100% effective in preventing candidiasis at 32 weeks' gestation and above and it would not represent good value for money compared with nystatin.



Lower panel shows detail from upper panel.
Incremental net health benefit of fluconazole compared with nystatin. Positive values indicate fluconazole would be preferred (if QALYs are valued at £20,000 each); negative values favour fluconazole over nystatin.

Figure HE016: One-way sensitivity analysis – fluconazole compared with nystatin at 28 weeks' gestation as a function of effectiveness of fluconazole in preventing infections

I.4.232 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (Figure HE018 and Figure HE017 – note the scales used in the cost-utility plots for 23 and 28 weeks' gestation are the same, and the scales used in 33 weeks' and 38 weeks' gestation are unique; this is done to show where most iterations of the model are plotted) provides further support for the above results. At lower gestational ages, regardless of antibiotic exposure, most iterations of the model result in reduced costs and increased QALYs when comparing nystatin with no prophylaxis. However, as gestational age

increases, most iterations of the model report similar results as above: the QALYs gained with nystatin decrease and the incremental costs move to zero. Eventually, at higher gestational ages, while nystatin is still associated with QALY gains, however small, it now has higher incremental costs in most iterations of the model. As previously discussed, this is because the rates of candidiasis become so low that any costs associated with a case, whether treating infection or costs secondary to long-term sequelae of infection move towards zero. However, the cost of prophylaxis remains, which makes both nystatin and fluconazole more expensive than no prophylaxis. It is at these gestational ages that the slightly higher costs associated with fluconazole and nystatin produce extraordinarily high ICER values as the QALY gains they produce are incredibly small fractions.

Probabilistic analysis comparing fluconazole with nystatin (Figure HE019) shows an obvious correlation between costs and QALYs. This is, as already described, a result of the predominance of the odds ratio for infection in determining model outputs: when ORs are sampled that disfavour nystatin and favour fluconazole, fluconazole becomes the optimal option in that iteration, and vice versa. These results further illustrate how, in most instances, the model favours whichever treatment is most effective in preventing cases of candidiasis.

The cost-effectiveness acceptability curve (CEAC; Figure HE018 and Figure HE017) is characteristic of an economic analysis with substantial correlation between costs and QALYs. In lower gestational ages, nystatin has approximately an 80% chance of being cost-effective with fluconazole occupying the remainder. This indicates that, at low gestational ages, the treatment that is most effective in preventing cases of infection will have the highest probability of being cost effective. However, as gestational age increases, the probability that no prophylaxis is the most cost-effective option begins to increase. This trend continues until no prophylaxis has a nearly 100% chance of being the most cost-effective option at the highest gestational ages. The reason why this switch occurs, albeit at slightly different gestational ages for babies with and without exposure to antibiotics, is due to the marginally higher costs associated with prophylaxis and the incredibly small QALY gains they produce. Together, these yield ICER values at the highest gestational ages in the millions of pounds per QALY.

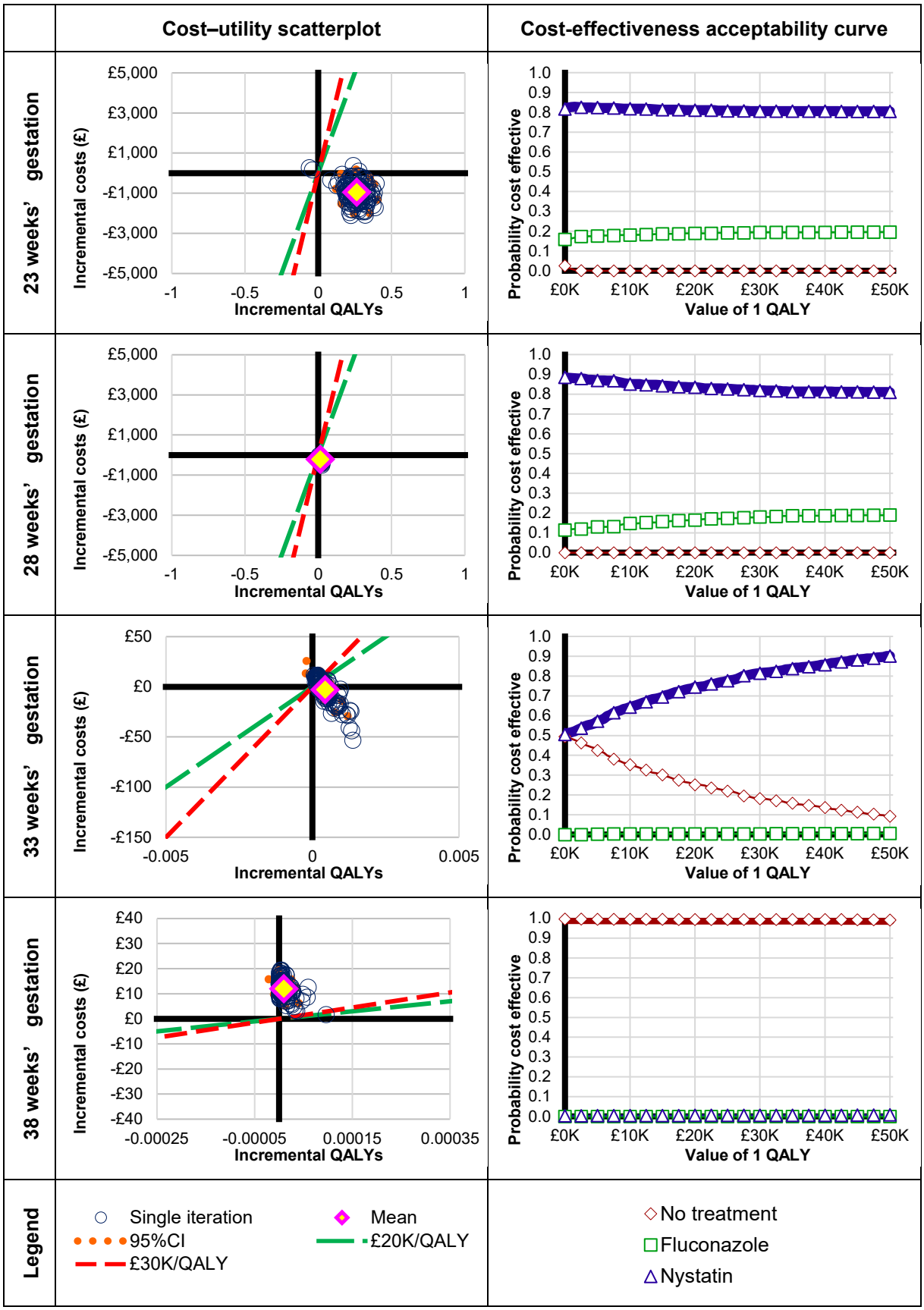


Figure HE017: Probabilistic sensitivity analysis – nystatin -v- no prophylaxis at indicative gestational ages without broad-spectrum antibiotics

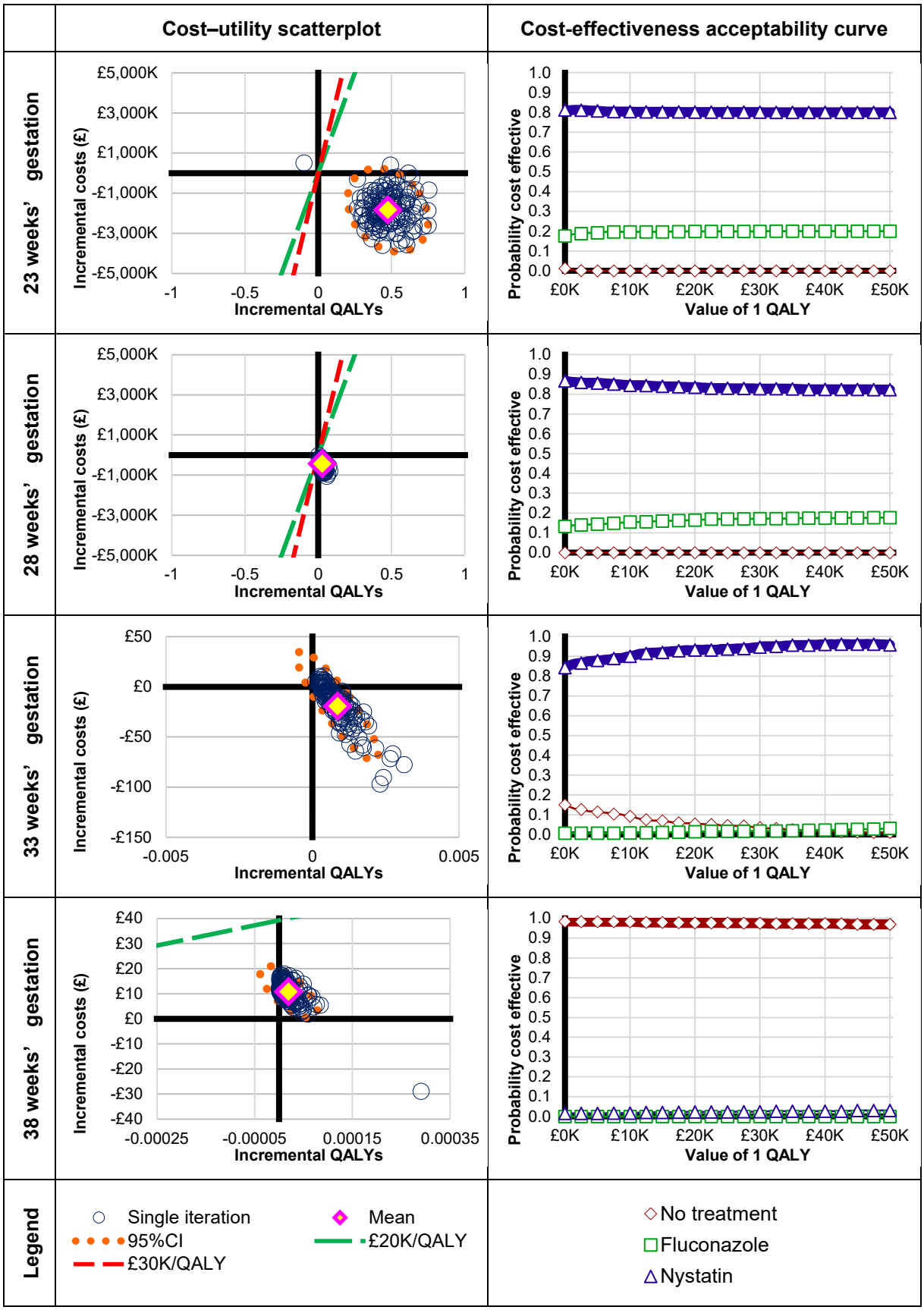


Figure HE018: Probabilistic sensitivity analysis – nystatin -v- no prophylaxis at indicative gestational ages with broad-spectrum antibiotics

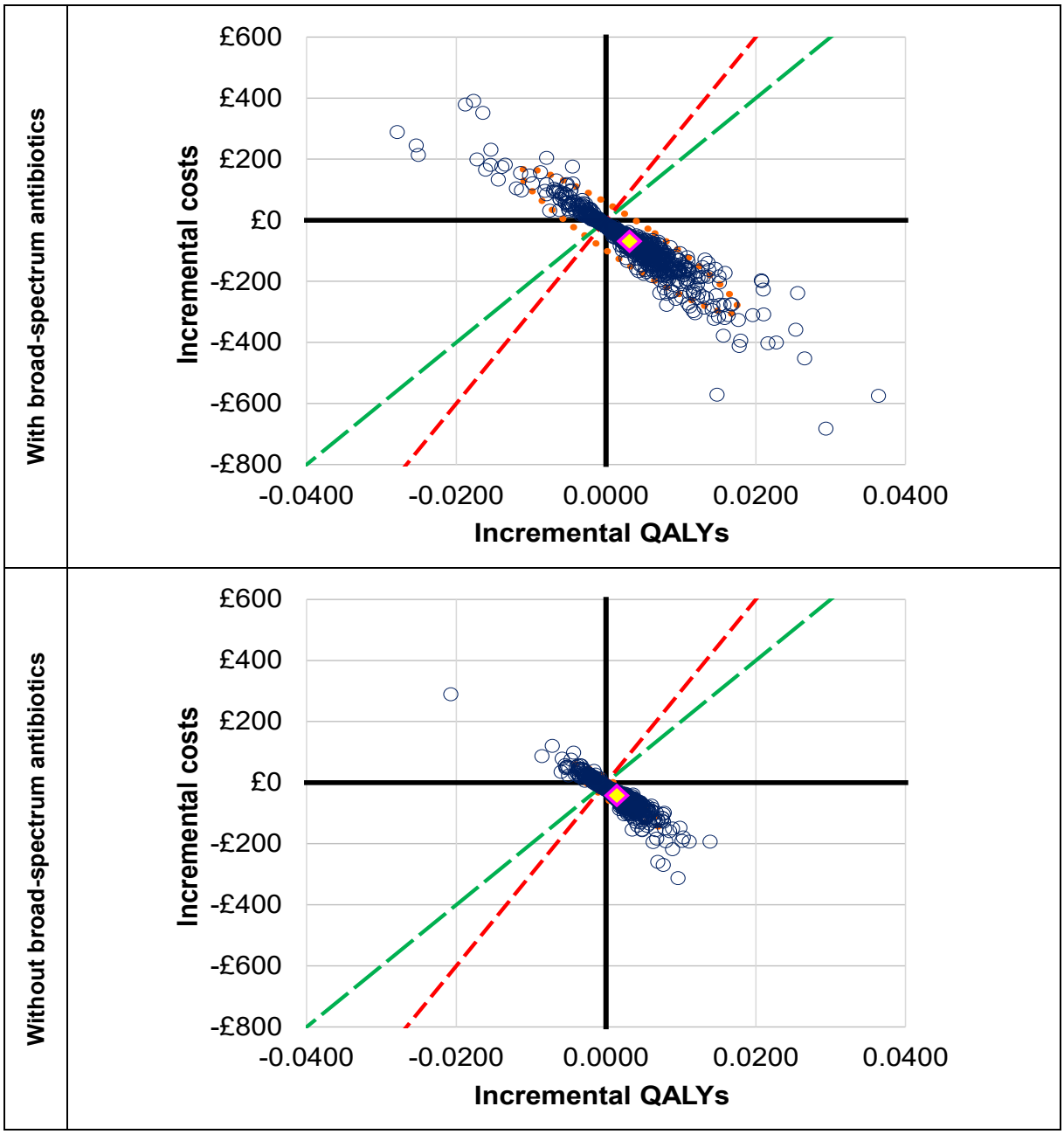


Figure HE019: Probabilistic sensitivity analysis – cost-utility scatterplot for nystatin -v- fluconazole at 28 weeks' gestation

I.4.3 Model validation

As discussed in I.3.3, we also had the results from the NMAs on mortality and length of stay. While it was not possible to incorporate these data directly in our model's inputs, we used them to validate the model's outputs.

I.4.3.1 Mortality

In order to assess how well our model predicts the empirical results synthesised in the NMA, we must first configure it to be as representative as possible of the underlying population and risks in the RCTs (which, it must be remembered, represent a slightly different population to the target of interest for us – all extremely low birthweight babies as opposed to neonates

who are starting antibiotics for suspected bacterial infection, respectively). In the RCTs, the rate of candidiasis in the control arms was about 20% (crude proportion of summed numerators and denominators: 0.197). This is a very high proportion, by present-day NHS standards (see I.3.2.3). We set our model to replicate this by selecting a gestational age of 25 weeks and increasing the probability of candidiasis so that an expected rate of 0.197 resulted. Then we calculated the odds of neonatal death in each arm, derived ratios, and compared these with the results of the clinical review.

Table HE020 tabulates results. It shows that all the model's predictions are comfortably within the 95% compatibility intervals from the evidence synthesis. The one apparent difference is that the model predicts that nystatin will result in marginally fewer deaths than fluconazole (because, at their point-estimates, the inputs suggest that it is associated with marginally fewer cases of invasive candidiasis) whereas, at their point-estimates, the RCT data indicate that there may be somewhat fewer deaths with fluconazole. However, unless there is some mechanism by which antifungals prevent deaths other than by preventing fungal infections (and the committee could not hypothesise any such effect), it is not plausible that one treatment should be better at preventing infections and the other should be better at preventing deaths. Therefore, simple sampling error in the RCTs is the most likely explanation for this apparent discrepancy, and our results show that an entirely coherent model can be fitted that is compatible with the empirical data at a 95% confidence level.

Table HE020: Mortality odds ratios from evidence review and predicted by the model

Source of evidence	Fluconazole -v- no prophylaxis	Nystatin -v- no prophylaxis	Nystatin -v- fluconazole
Direct pairwise data[a]	0.73 (0.54, 0.98)	0.84 (0.57, 1.23)	1.43 (0.63, 3.22)
Network meta-analysis[b]	0.71 (0.53, 0.95)	0.88 (0.61, 1.28)	1.24 (0.79, 1.94)
Model results[c]	0.87	0.85	0.98

(a) Values in parenthesis are 95% confidence intervals
(b) Values in parenthesis are 95% credible intervals
(c) For 25-week gestational age and an underlying probability of candidiasis of 0.197

When we revert to inputs that are more reflective of our decision-problem (with lower rates of expected candidiasis and, hence, fewer deaths), the odds ratios for death become closer to 1 for all comparisons, and may exceed the compatibility intervals in Table HE020. However, we would not necessarily expect our model results to match those observed in a different population.

I.4.2.2 Length of stay

As with mortality, we use the length of stay results from the clinical review, both direct pairwise and NMA, to validate the predictions by the model. We do this by comparing the mean difference in length of stay between treatments predicted by the model against the observed data. To do so, we configure the model in the same way as above, in attempt to approximate the population reflected in the RCTs.

As detailed in Table HE021, the values predicted by the model always fall within the 95% compatibility interval for both the direct pairwise results and the NMA results. Our model tends to estimate somewhat greater differences between prophylaxis and none, and somewhat smaller differences between the 2 agents, than are seen in the RCTs. However, as with mortality, it seems implausible that large differences in length of stay should arise without large differences in candidiasis rates. In this case, our uncertainty in the empirical data is exacerbated by the fact that only 5 RCTs report length of hospitalisation, and some of

these date back to the 1980s. Despite these uncertainties, our model is at least compatible with the observed data, at a 95% compatibility level.

Table HE021: Length of stay mean difference from NMA and predicted by the model

	Fluconazole -v- no prophylaxis	Nystatin -v- no prophylaxis	Nystatin -v- fluconazole
Direct pairwise data[a]	−0.32 (−3.95, 3.30)	−2.51 (−6.93, 1.90)	−1.00 (−7.34, 5.34)
Network meta-analysis[b]	−0.41 (−3.98, 3.14)	−2.21 (−6.27, 1.86)	−1.80 (−6.46, 2.87)
Model results[c]	−3.31	−3.79	−0.48

(a) Values in parenthesis are 95% confidence intervals
(b) Values in parenthesis are 95% credible intervals
(c) For 25-week gestational age and an underlying probability of candidiasis of 0.197

I.5 Discussion

I.5.1 Principal findings

In the base case of the model, for gestational ages between 22 weeks and 33 weeks (if no broad-spectrum antibiotics are used) or 34 weeks (if they are), nystatin dominates both no prophylaxis and fluconazole – that is, it is associated with more QALYs gained and lower costs. These differences are more pronounced at lower gestational ages. Above 30 weeks' gestation, the difference in costs and QALYs is very small. When comparing fluconazole and nystatin, sensitivity analysis shows that the odds ratio estimating the relative likelihood of infection compared with placebo for the 2 prophylactic treatments is by far the greatest contributor to model uncertainty.

These results arise because our model predicts that the lifetime discounted costs and consequences associated with a case of neonatal candidiasis far outweigh the relatively minor costs of the drugs, which are the only costs in the model associated with giving antifungal prophylaxis. The model estimates that an average case of neonatal candidiasis at a gestational age of 28 weeks adds just under £40,000 to lifetime expected costs and reduces quality-adjusted life-expectancy by over 2.6 years. This implies society should be prepared to pay over £90,000 per case of neonatal invasive candidiasis prevented.

I.5.2 Strengths

This is the first economic analysis of this decision problem. Its development was informed by a multidisciplinary committee of clinical and patient experts who advised on structure, assumptions and potential datasources, and provided validation of model outputs. Treatment effects are drawn from a novel network meta-analysis, which is the first analysis synthesising all relevant data. The model is able to explore a wide range of scenarios, reflecting neonates with a variety of risk factors, as an appreciation of these factors is likely to be important for decision-making.

I.5.3 Limitations

Our model is driven by three probabilities, each with their own limitations: 1) probability of candidiasis by gestational age 2) probability of death by gestational age 3) probability of neurodevelopmental impairment by gestational age.

Regarding the first point, the model relies on data from a US study (Benjamin et al. 2010) to estimate the extent to which the probability of candidiasis is affected by gestational age.

Although we apply this relative effect to UK-specific incidence data (Oeser et al. 2014), it is possible that the relationship between gestational age and risk of candidiasis is different in the UK. However, no such data exist, and the committee agreed that approach we took was a reasonable substitution.

With regard to the second point, the model again relies on data from a US study (Benjamin et al. 2006) to calculate the odds ratio of death for invasive candidiasis versus none. Again, we apply this relative effect to UK-specific absolute data (ONS), but it would be preferable to use UK data throughout. However, we could not identify a UK study that also has a control arm by which to calculate the relative effect of candidiasis on mortality.

With regard to the third point, data for specific outcomes associated with candidiasis would be preferable. Such data are reported in 1 study from the USA (Benjamin et al., 2006); however, in this instance, the committee agreed that using this datasource would impose too many problems. First, as noted in I.3.3.2, the outcomes they report are not mutually exclusive, and no information is provided as how to how multiple outcomes coexist. Additionally, we would need to build lifetime models estimating lifetime costs and QALYs associated with outcomes which occur at birth. Such data are sparsely available and would require extrapolation from other sources, for instance extrapolating utility values from blind adults to blind children. The committee agreed that extrapolations of this type would have an uncertain impact on model results. Therefore, rather than making numerous assumptions and extrapolating from other populations, the committee agreed that it was better to model neurodevelopmental impairment as an overarching outcome. Data on incidence of cerebral palsy by gestational age were considered a reasonable proxy for the relative effect of prematurity on incidence of neurodevelopmental sequelae. We obtained the proportional severity of disability (mild, moderate or severe) from another UK population-based cohort study of extremely premature babies. The model would be improved if data regarding proportional severity secondary to candidiasis existed. However, our sensitivity analyses suggest that the model's results are relatively insensitive to any inaccuracy, in this area.

The costs associated with candidiasis represent a further limitation of the model. While informal searches were performed to identify the costs associated with candidiasis, we did not identify any credible estimates. One factor affecting this is most infants who develop candidiasis weigh less than 1500 grams and, as such, are likely to require lengthy hospital stays regardless of whether they develop infection. This fact makes presenting results that provide an estimate of increased costs or increased length of stay directly a result of candidiasis difficult to do. Therefore, in order to estimate the impact of infection, we relied on data for length of stay from infants with late onset GBS infection.

As was the case in the de novo model developed for preterm prelabour rupture of membranes (see evidence review C), the committee was keen for the model to incorporate estimates of the impact of infections and their fatal and nonfatal sequelae on carers and families. However, we were unable to identify suitable data for us to quantify these factors. In any event, being able to capture this impact would only bolster the results of the model and the committee's recommendation. This is because the model favours treatments that lead to a reduction in cases of candidiasis, as cases are both expensive to treat and result in QALY losses. If the impacts of infections and their fatal and nonfatal sequelae on carers and families could be modelled, we can anticipate a larger financial burden due to candidiasis and larger QALY losses. This would be unlikely to have a material influence on model results, which already show that candidiasis is worth preventing, even when the risk of it is extremely low.

Finally, it is a limitation of our model that we only incorporate 1 output from the NMA, incidence of infection, when we had direct empirical evidence on 2 further outputs, mortality and length of stay. However, as noted in I.3.3, incorporating these data as inputs would have

required assumptions about baseline probabilities which would have been in conflict with the flexible approach we needed. Instead we developed a model using direct evidence of treatment effects in preventing fungal infection alone and, by way of validation, compared its outputs with the observed data for the other outcomes. As the model's predictions were consistent with the RCTs' effect estimates (see I.4.3), our confidence in the validity of the approach was reinforced.

I.5.4 Comparison with other published economic analyses

Our systematic review of published economic analyses identified no studies of relevance to this question.

I.6 Critical appraisal of original model

2 **Table HE022: Economic evaluation checklist**

Category	Rating	Comments
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	Sensitivity analysis at 1.5%
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Partly	Specific outcomes associated with candidiasis would enhance model; using NDI stratified by severity as a proxy is a reasonable alternative
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	Data on association between gestational age and candidiasis come from a US study from 2010. A more recent UK study would enhance model, but in absence of any this is a reasonable alternative
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Partly	Specific resource data associated with candidiasis would enhance model; using LOGBS data as a proxy is a reasonable alternative to estimate the impacts of infection
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	

Category	Rating	Comments
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

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1 Appendix J – Excluded studies

2 Clinical studies

Study	Reason
Adelman, R D; Wirth, F; Rubio, T (1987) A controlled study of the nephrotoxicity of mezlocillin and amikacin in the neonate. American journal of diseases of children (1960) 141(11): 1175-8	- Study does not include population of interest *[States infants with suspected infection but does not reported age]*
Adelman, R D; Wirth, F; Rubio, T (1987) A controlled study of the nephrotoxicity of mezlocillin and gentamicin plus ampicillin in the neonate. The Journal of pediatrics 111(6pt1): 888-93	- Study does not include population of interest *[Study does not state age of neonates]*
African Neonatal Sepsis Trial (AFRINEST), group, Tshefu, Antoinette, Lokangaka, Adrien et al. (2015) Simplified antibiotic regimens compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with clinical signs of possible serious bacterial infection when referral is not possible: a randomised, open-label, equivalence trial. Lancet (London, England) 385(9979): 1767-1776	- Community-based antibiotic regimes. Not relevant to UK practice
Agarwal, Ghanshyam, Rastogi, Alok, Pyati, Suma et al. (2002) Comparison of once-daily versus twice-daily gentamicin dosing regimens in infants > or = 2500 g. Journal of perinatology : official journal of the California Perinatal Association 22(4): 268-74	- Study does not contain outcomes of interest
Ahangarkani, F., Shokohi, T., Rezai, M.S. et al. (2020) Epidemiological features of nosocomial candidaemia in neonates, infants and children: A multicentre study in Iran. Mycoses 63(4): 382-394	- Study does not contain outcomes of interest
Alinejad, S., Yousefichaijan, P., Rezagholizamenjany, M. et al. (2018) Nephrotoxic effect of gentamicin and amikacin in neonates with infection. Nephro-Urology Monthly 10(2): e58580	- Study does not contain outcomes of interest
Allen, T.R. and Da Silva, O.P. (2003) Choice of antibiotics in late neonatal sepsis in the extremely low birth weight infant. Canadian Journal of Infectious Diseases 14(1): 28-31	- Not a relevant study design *[Observational study that does not report information on antibiotic resistance]*

Study	Reason
Alsaedi, SA (2003) Once daily gentamicin dosing in full term neonates. Saudi medical journal 24(9): 978-981	- Study does not contain outcomes of interest
Autmizguine, Julie, Smith, P Brian, Prather, Kristi et al. (2018) Effect of fluconazole prophylaxis on Candida fluconazole susceptibility in premature infants. The Journal of antimicrobial chemotherapy 73(12): 3482-3487	- Follow-up study to Benjamin 2014 that does not contain any new relevant information
Aydemir, Cumhur, Oguz, Serife Suna, Dizdar, Evrim Alyamac et al. (2011) Randomised controlled trial of prophylactic fluconazole versus nystatin for the prevention of fungal colonisation and invasive fungal infection in very low birth weight infants. Archives of disease in childhood. Fetal and neonatal edition 96(3): f164-8	- Study does not include population of interest *[Babies <72 hours of age]*
Baqui, Abdullah H, Saha, Samir K, Ahmed, A S M Nawshad Uddin et al. (2015) Safety and efficacy of alternative antibiotic regimens compared with 7 day injectable procaine benzylpenicillin and gentamicin for outpatient treatment of neonates and young infants with clinical signs of severe infection when referral is not possible: a randomised, open-label, equivalence trial. The Lancet. Global health 3(5): e279-87	- Community-based antibiotic regimes. Not relevant to UK practice
Baqui, Abdullah H, Saha, Samir Kumar, Ahmed, A S M Nawshad Uddin et al. (2013) Safety and efficacy of simplified antibiotic regimens for outpatient treatment of serious infection in neonates and young infants 0-59 days of age in Bangladesh: design of a randomized controlled trial. The Pediatric infectious disease journal 32suppl1: 12-8	- Community-based antibiotic regimes. Not relevant to UK practice
Batra, A and Kler, N (2009) Antibiotic therapy in neonatal sepsis: cochrane reviews. Journal of neonatology 23(1): 78-79	- Not a relevant study design *[Summary of systematic reviews]*
Benjamin Jr., D.K., Hudak, M.L., Duara, S. et al. (2014) Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: A randomized clinical trial. JAMA - Journal of the American Medical Association 311(17): 1742-1749	- RCT for antifungal treatment that does not meet the methods stated in the protocol *[Use of antifungals for preterm babies. Babies did not need to be receiving antibiotic treatment for suspected infection]*

Study	Reason
Bennet, R, Eriksson, M, Nord, CE et al. (1986) Fecal bacterial microflora of newborn infants during intensive care management and treatment with five antibiotic regimens. Pediatric infectious disease 5(5): 533-539	- Not a relevant study design *[Observational study that does not report antibiotic resistance outcomes]*
Bordbar, A., Mazouri, A., Kashaki, M. et al. (2017) Standard multiple and single daily dosing of amikacin in premature infants. Iranian Journal of Neonatology 8(4): 57-64	- Study does not contain outcomes of interest
Burman, L G, Berglund, B, Huovinen, P et al. (1993) Effect of ampicillin versus cefuroxime on the emergence of beta-lactam resistance in faecal Enterobacter cloacae isolates from neonates. The Journal of antimicrobial chemotherapy 31(1): 111-6	- Study does not include population of interest *[States infants being discharged from neonatal unit but age is not reported]*
Cailes, B., Kortsalioudaki, C., Buttery, J. et al. (2018) Epidemiology of UK neonatal infections: The neonIN infection surveillance network. Archives of Disease in Childhood: Fetal and Neonatal Edition 103(6): F547-F553	- Not a relevant study design *[Observational study that does not report antibiotic resistance outcomes]*
Cailes, Benjamin, Kortsalioudaki, Christina, Buttery, Jim et al. (2018) Antimicrobial resistance in UK neonatal units: neonIN infection surveillance network. Archives of disease in childhood. Fetal and neonatal edition 103(5): f474-f478	- Not a relevant study design *[Non-comparative observational study]*
Ceriani Cernadas, Jose M, Fernandez Jonusas, Silvia, Marquez, Maritza et al. (2014) Clinical outcome of neonates with nosocomial suspected sepsis treated with cefazolin or vancomycin: a non-inferiority, randomized, controlled trial. Archivos argentinos de pediatria 112(4): 308-14	- Study not reported in English
Chaudhari, Sudha, Suryawanshi, Pradeep, Ambardekar, Shrikant et al. (2004) Safety profile of ciprofloxacin used for neonatal septicemia. Indian pediatrics 41(12): 1246-51	- Not a relevant study design *[Observational study that does not report antibiotic resistance outcomes]*
Chotigeat, U; Narongsanti, A; Ayudhya, D P (2001) Gentamicin in neonatal infection: once versus twice daily dosage. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 84(8): 1109-15	- Study does not include population of interest *[Babies with suspected early-onset infection]*

Study	Reason
Coscia, A, Maiorca, D, Martano, C et al. (2008) Use of netilmicin once or twice daily in preterm newborns: evaluation of nephrotoxicity by urinary alpha1-microglobulin and retinol binding protein. Journal of chemotherapy (florence, italy) 20(3): 324-326	- Not a relevant study design *[Non-RCT study]*
de Louvois, J; Dagan, R; Tessin, I (1992) A comparison of ceftazidime and aminoglycoside based regimens as empirical treatment in 1316 cases of suspected sepsis in the newborn. European Society for Paediatric Infectious Diseases--Neonatal Sepsis Study Group. European journal of pediatrics 151(12): 876-84	- Study does not include population of interest *[Median age was within the range for early-onset infection. No information about how many babies with late-onset infection were included]*
Degefie Hailegebriel, Tedbabe, Mulligan, Brian, Cousens, Simon et al. (2017) Effect on Neonatal Mortality of Newborn Infection Management at Health Posts When Referral Is Not Possible: A Cluster-Randomized Trial in Rural Ethiopia. Global health, science and practice 5(2): 202-216	- Community-based antibiotic regimes. Not relevant to UK practice
Demirel, Gamze, Celik, Istemi Han, Erdeve, Omer et al. (2013) Prophylactic Saccharomyces boulardii versus nystatin for the prevention of fungal colonization and invasive fungal infection in premature infants. European journal of pediatrics 172(10): 1321-6	- Study does not include population of interest *[Babies aged <72 hours]*
Duby, Jessica; Lassi, Zohra S; Bhutta, Zulfiqar A (2019) Community-based antibiotic delivery for possible serious bacterial infections in neonates in low- and middle-income countries. The Cochrane database of systematic reviews 4: cd007646	- Community-based antibiotic regimes. Not relevant to UK practice *[Systematic review of community-based antibiotics]*
El-barbary, M.N.; Ismail, R.I.H.; Ibrahim, A.A.A. (2015) Gentamicin extended interval regimen and ototoxicity in neonates. International Journal of Pediatric Otorhinolaryngology 79(8): 1294-1298	- Not a relevant study design *[Non-RCT study of effectiveness]*
Engle, W D, Jackson, G L, Sendelbach, D et al. (2000) Neonatal pneumonia: comparison of 4 vs 7 days of antibiotic therapy in term and near-term infants. Journal of perinatology : official journal of the California Perinatal Association 20(7): 421-6	- Study does not include population of interest *[Babies with symptoms of early-onset infection]*

Study	Reason
Engle, William D, Jackson, Gregory L, Sendelbach, Dorothy M et al. (2003) Pneumonia in term neonates: laboratory studies and duration of antibiotic therapy. Journal of perinatology : official journal of the California Perinatal Association 23(5): 372-7	- Study does not include population of interest *[Babies with symptoms of early-onset infection]*
Fjalstad, Jon Widding, Esaiassen, Eirin, Juvet, Lene Kristine et al. (2018) Antibiotic therapy in neonates and impact on gut microbiota and antibiotic resistance development: a systematic review. The Journal of antimicrobial chemotherapy 73(3): 569-580	- Systematic review. Reference list checked for possible includes
Giapros, VI, Andronikou, S, Cholevas, VI et al. (1995) Renal function in premature infants during aminoglycoside therapy. Pediatric nephrology (Berlin, Germany) 9(2): 163-166	- Study does not include population of interest *[Babies with suspected early-onset infection]*
Giustardi, A and Coppola, G (1992) Comparison of plasma concentrations of amoxicillin administered by oral and venous routes in neonatal bacterial colonizations. Pediatria medica e chirurgica [Medical and surgical pediatrics] 14(4): 447-449	- Study not reported in English
Gordon Adrienne, Jeffery Heather E (2005) Antibiotic regimens for suspected late onset sepsis in newborn infants. Cochrane Database of Systematic Reviews: Reviews issue3	- Systematic review. Reference list checked for possible includes
Gordon, A and Jeffery, H E (2005) Antibiotic regimens for suspected late onset sepsis in newborn infants. The Cochrane database of systematic reviews: cd004501	- Systematic review. Reference list checked for possible includes
Guadalupe Vasquez-Mendoza, Ma, Vargas-Origel, Arturo, Del Carmen Ramos-Jimenez, Aurelia et al. (2007) Efficacy and renal toxicity of one daily dose of amikacin versus conventional dosage regime. American journal of perinatology 24(2): 141-6	- Study does not include population of interest *[Mean age was within the time period for early-onset infection]*
Gwee, A., Cranswick, N., McMullan, B. et al. (2019) Continuous versus intermittent vancomycin infusions in infants: A randomized controlled trial. Pediatrics 143(2): e20182179	- Study does not contain outcomes of interest

Study	Reason
Hagen, I and Oymer, K (2009) Pharmacological differences between once and twice daily gentamicin dosage in newborns with suspected sepsis. Pharmacy world and science 31: 18-23	- Not a relevant study design *[Observational study that does not reported antibacterial resistance outcomes]*
Hall, M A, Ducker, D A, Lowes, J A et al. (1988) A randomised prospective comparison of cefotaxime versus netilmicin/penicillin for treatment of suspected neonatal sepsis. Drugs 35suppl2: 169-77	- Study does not include population of interest *[Included babies with suspected infection but mean age was within the time period for early-onset infection in both groups]*
Hammerberg, O, Elder, D, Richardson, H et al. (1986) Staphylococcal resistance to aminoglycosides before and after introduction of amikacin in two teaching hospitals. Journal of clinical microbiology 24(4): 629-32	- Study does not include population of interest *[Observational study reporting antimicrobial resistance but results are for neonatal and adult wards combined]*
Hayani, K C, Hatzopoulos, F K, Frank, A L et al. (1997) Pharmacokinetics of once-daily dosing of gentamicin in neonates. The Journal of pediatrics 131(1pt1): 76-80	- Study does not include population of interest *[Babies with suspected early-onset infection]*
Hemels, Marieke A C, van den Hoogen, Agnes, Verboon-Maciolek, Malgorzata A et al. (2012) Shortening the antibiotic course for the treatment of neonatal coagulase-negative staphylococcal sepsis: fine with three days?. Neonatology 101(2): 101-5	- Not a relevant study design *[Observational study which does not report antibacterial resistance outcomes]*
Holton, A F; Hall, M A; Lowes, J A (1989) Antibiotic exposure delays intestinal colonization by Clostridium difficile in the newborn. The Journal of antimicrobial chemotherapy 24(5): 811-7	- Study does not include population of interest *[States that neonates were included but no information about their age]*
Howell, A., Barfield, C., Bourchier, D. et al. (2009) Oral nystatin prophylaxis and neonatal fungal infections. Archives of Disease in Childhood: Fetal and Neonatal Edition 94(6): f429-f433	- Not a relevant study design *[Observational study that does not report resistance outcomes]*
Jaiswal, Nishant, Singh, Meenu, Kondel, Ritika et al. (2016) Feasibility and efficacy of gentamicin for treating neonatal sepsis in community-based settings: a systematic review. World journal of pediatrics : WJP 12(4): 408-414	- Community-based antibiotic regimes. Not relevant to UK practice *[Systematic review of community-based antibiotics]*

Study	Reason
Kaguelidou, Florentia, Turner, Mark A, Choonara, Imti et al. (2013) Randomized controlled trials of antibiotics for neonatal infections: a systematic review. British journal of clinical pharmacology 76(1): 21-9	- Systematic review. Reference list checked for possible includes
Kaufman, D., Boyle, R., Hazen, K.C. et al. (2001) Fluconazole prophylaxis against fungal colonization and infection in preterm infants. New England Journal of Medicine 345(23): 1660-1666	- Study does not include population of interest *[Babies treated with antifungals but mean age at enrollment was within the time period for early-onset infection]*
Kaufman, D., Boyle, R., Hazen, K.C. et al. (2005) Twice weekly fluconazole prophylaxis for prevention of invasive Candida infection in high-risk infants of <1000 grams birth weight. Journal of Pediatrics 147(2): 172-179	- Study does not include population of interest *[Babies given antifungal treatment but median age was within the time period for early-onset infection]*
Kaufman, D.A., Morris, A., Gurka, M.J. et al. (2014) Fluconazole prophylaxis in preterm infants: A multicenter case-controlled analysis of efficacy and safety. Early Human Development 90(suppl1): 87-s90	- Not a relevant study design *[Non-RCT study of effectiveness]*
Keij, F.M., Kornelisse, R.F., Hartwig, N.G. et al. (2019) RAIN study: A protocol for a randomised controlled trial evaluating efficacy, safety and cost-effectiveness of intravenous-to-oral antibiotic switch therapy in neonates with a probable bacterial infection. BMJ Open 9(7): e026688	- Not a peer-reviewed publication *[Protocol for RAIN study]*
Kicklighter, S.D., Springer, S.C., Cox, T. et al. (2001) Fluconazole for prophylaxis against candidal rectal colonization in the very low birth weight infant. Pediatrics 107(2): 293-298	- Study does not include population of interest *[Excluded babies admitted to the NICU over 72 hours of age]*
Kirpal, Harita, Gathwala, Geeta, Chaudhary, Uma et al. (2016) Prophylactic fluconazole in very low birth weight infants admitted to neonatal intensive care unit: randomized controlled trial. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 29(4): 624-8	- Study does not include population of interest *[Babies with suspected early-onset infection. Must have already been given antibiotics before starting antifungals]*

Study	Reason
Kotze, A.; Bartel, P.R.; De Sommers, K. (1999) Once versus twice daily amikacin in neonates: Prospective study on toxicity. Journal of Paediatrics and Child Health 35(3): 283-286	- Study does not include population of interest *[Babies with suspected early-onset infection]*
Krediet, T G; Fleer, A; Gerards, L J (1993) Development of resistance to aminoglycosides among coagulase-negative staphylococci and enterobacteriaceae in a neonatal intensive care unit. The Journal of hospital infection 24(1): 39-46	- Study does not include population of interest *[Study includes babies admitted to a NICU but no information about age]*
Krishnan, L and George, S A (1997) Gentamicin therapy in preterms: a comparison of two dosage regimens. Indian pediatrics 34(12): 1075-80	- Study does not include population of interest *[Median age was within the time period for early-onset infection]*
Le, Jennifer, Nguyen, Thuy, Okamoto, Mark et al. (2008) Impact of empiric antibiotic use on development of infections caused by extended-spectrum beta-lactamase bacteria in a neonatal intensive care unit. The Pediatric infectious disease journal 27(4): 314-8	- Study does not contain outcomes of interest
Lee, SJ and Park, EA (2005) Efficacy and Safety of Amoxicillin-sulbactam and Ampicillin-sulbactam in Full Term Neonates. Journal of the korean society of neonatology 12(1): 17-24	- Study not reported in English
Leverger, Guy, Timsit, Jean-Francois, Milpied, Noel et al. (2019) Use of Micafungin for the Prevention and Treatment of Invasive Fungal Infections in Everyday Pediatric Care in France: Results of the MYRIADE Study. The Pediatric infectious disease journal 38(7): 716-721	- Study does not contain outcomes of interest *Observational study that does not report resistance outcomes*
Levin, GS, Jesurun, CA, Ipsen, MA et al. (2003) Neonatal suspected sepsis: a cost comparison of 2 vs. 3 days of antibiotic therapy. Pediatric research 53: 137	- Conference abstract
Lokangaka, A., Bauserman, M., Coppieters, Y. et al. (2018) Simplified antibiotic regimens for treating neonates and young infants with severe infections in the Democratic Republic of Congo: A comparative efficacy trial. Maternal Health, Neonatology and Perinatology 4(1): 8	- Community-based antibiotic regimes. Not relevant to UK practice

Study	Reason
Lönnerholm, G; Bengtsson, S; Ewald, U (1982) Oral pivampicillin and amoxycillin in newborn infants. Scandinavian journal of infectious diseases 14(2): 127-130	- Not a relevant study design *[Non-RCT study of effectiveness]*
Manzoni, P., Arisio, R., Mostert, M. et al. (2006) Prophylactic fluconazole is effective in preventing fungal colonization and fungal systemic infections in preterm neonates: A single-center, 6-year, retrospective cohort study. Pediatrics 117(1): e22-e32	- Not a relevant study design *[Non-comparative observational study]*
Manzoni, P., Farina, D., Leonessa, M.L. et al. (2006) Use of prophylactic fluconazole in a neonatal intensive care unit: Efficacy is similar to that described in adult high-risk surgical patients. Critical Care 10(1): 402	- Not a peer-reviewed publication *[Letter to the editor]*
Manzoni, P., Stolfi, I., Pugni, L. et al. (2007) A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. New England Journal of Medicine 356(24): 2483-2495	- Study does not include population of interest *[Babies with suspected early-onset infection]*
Marks, S, Marks, M I, Dupont, C et al. (1978) Evaluation of three antibiotic programs in newborn infants. Canadian Medical Association journal 118(6): 659-62	- Study does not contain outcomes of interest
Mathur, N B; Kharod, Prarthana; Kumar, Surinder (2015) Evaluation of duration of antibiotic therapy in neonatal bacterial meningitis: a randomized controlled trial. Journal of tropical pediatrics 61(2): 119-25	- Study does not contain a relevant intervention *[Examines use of antibiotics for neonatal infection but does not state which antibiotics and doses were used in the trial]*
Mathur, N B and Murugesan, A (2018) Comparison of Four Days Versus Seven Days Duration of Antibiotic Therapy for Neonatal Pneumonia: A Randomized Controlled Trial. Indian journal of pediatrics 85(11): 963-967	- Study does not include population of interest *[Neonates with pneumonia without positive blood culture]*
McCracken, G H Jr; Mize, S G; Threlkeld, N (1980) Intraventricular gentamicin therapy in gram-negative bacillary meningitis of infancy. Report of the Second Neonatal Meningitis Cooperative Study Group. Lancet (London, England) 1(8172): 787-91	- Study does not include population of interest *[Includes neonates and children up to 1 year. Results for neonates not reported separately]*

Study	Reason
McCracken, G H Jr, Threlkeld, N, Mize, S et al. (1984) Moxalactam therapy for neonatal meningitis due to gram-negative enteric bacilli. A prospective controlled evaluation. JAMA 252(11): 1427-32	- Study does not include population of interest *[Children up to 1 year. Results for neonates not reported separately]*
McCracken, GJ, Threlkeld, N, Mize, S et al. (1984) Moxalactam therapy for neonatal meningitis due to gram-negative enteric bacilli. JAMA 252: 1427-1432	- Study does not include population of interest *[Children up to 1 year. Results for neonates not reported separately]*
McCrossan, Brian A, McHenry, Elaine, O'Neill, Fiona et al. (2007) Selective fluconazole prophylaxis in high-risk babies to reduce invasive fungal infection. Archives of disease in childhood. Fetal and neonatal edition 92(6): f454-8	- Study does not include population of interest *[Babies given antifungals but not necessarily when given antibiotics]* - Not a relevant study design *[Observational study which does not report antifungal resistance outcomes]*
Miall-Allen, V M; Whitelaw, A G; Darrell, J H (1988) Ticarcillin plus clavulanic acid (Timentin) compared with standard antibiotic regimes in the treatment of early and late neonatal infections. The British journal of clinical practice 42(7): 273-9	- Study does not contain outcomes of interest
Narang, A; Dutta, S; Choudhard, G (2005) Randomized Controlled Trial of 7-Day Versus 14-Day Antibiotic Regimes for Neonatal Sepsis. Pediatric academic societies annual meeting; 2005 may 14-17; washington DC, united states	- Study does not include population of interest
Nelson, JD and McCracken, GH (1973) Clinical pharmacology of carbenicillin and gentamicin in the neonate and comparative efficacy with ampicillin and gentamicin. Pediatrics 52(6): 801-812	- Study does not contain outcomes of interest *[Observational study which does not report antibiotic resistance outcomes]*
Nestaas, E., Bangstad, H.-J., Sandvik, L. et al. (2005) Aminoglycoside extended interval dosing in neonates is safe and effective: A meta-analysis. Archives of Disease in Childhood: Fetal and Neonatal Edition 90(4): f294-f300	- Systematic review. Reference list checked for possible includes
Pacifici, G.M. (2009) Peak and trough concentrations of gentamicin in the neonate: A	- Study does not contain outcomes of interest

Study	Reason
review of the literature. Current Pediatric Reviews 5(1): 2-7	*[Systematic review which did not cover the outcomes of interest]*
Pawlotsky, F, Thomas, A, Kergueris, M F et al. (1998) Constant rate infusion of vancomycin in premature neonates: a new dosage schedule. British journal of clinical pharmacology 46(2): 163-7	- Not a relevant study design *[Non-RCT study]*
Robati Anaraki, Mahmoud; Nouri-Vaskeh, Masoud; Abdoli Oskoei, Shahram (2020) Fluconazole Prophylaxis Against Invasive Candidiasis in Very Low and Extremely Low Birth Weight Preterm Neonates: A Systematic Review and Meta-Analysis. Clinical and experimental pediatrics	- Systematic review. Reference list checked for possible includes
Rajchgot, P, Prober, CG, Soldin, S et al. (1984) Aminoglycoside related nephrotoxicity in the premature newborn. Clinical pharmacology and therapeutics 35: 394-401	- Study does not contain outcomes of interest
Rao Shripada C, Srinivasjois Ravisha, Hagan Ronald, Ahmed Mohmed (2011) One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Cochrane Database of Systematic Reviews: Reviews issue11	- Systematic review. Reference list checked for possible includes
Rao, Shripada C; Srinivasjois, Ravisha; Moon, Kwi (2016) One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. The Cochrane database of systematic reviews 12: cd005091	- Systematic review. Reference list checked for possible includes
Reed, MD, Kliegman, RM, Yamashita, TS et al. (1990) Clinical pharmacology of imipenem and cilastatin in premature infants during the first week of life. Antimicrobial agents and chemotherapy 34(6): 1172-1177	- Not a relevant study design *[Non-randomised trial]*
Saini, Shiv Sajan, Dutta, Sourabh, Ray, Pallab et al. (2011) Short course versus 7-day course of intravenous antibiotics for probable neonatal septicemia: a pilot, open-label, randomized controlled trial. Indian pediatrics 48(1): 19-24	- Study does not include population of interest *[Babies with suspected infection but median age was within the time period for early-onset infection]*

Study	Reason
Seale, Josephine V, Hutchinson, Richard A, Fleming, Paul F et al. (2018) Does antibiotic choice for the treatment of suspected late-onset sepsis in premature infants determine the risk of developing necrotising enterocolitis? A systematic review. Early human development 123: 6-10	- Study does not contain outcomes of interest *[Systematic review that does not contain outcomes of interest]*
Shabuj, MKH, Moni, SC, Shaha CK et al. (2017) Gentamicin in newborn sepsis: once-daily versus twice-daily dose. Bangladesh medical research council bulletin 43(2): 82-86	- Not a relevant study design *[non-RCT trial]*
Shah Sachin S, Ohlsson Arne, Shah Vibhuti S (2012) Intraventricular antibiotics for bacterial meningitis in neonates. Cochrane Database of Systematic Reviews: Reviews issue7	- Systematic review. Reference list checked for possible includes
Shah, Sachin S; Ohlsson, Arne; Shah, Vibhuti S (2012) Intraventricular antibiotics for bacterial meningitis in neonates. The Cochrane database of systematic reviews: cd004496	- Duplicate reference
Skopnik, H, Wallraf, R, Nies, B et al. (1992) Pharmacokinetics and antibacterial activity of daily gentamicin. Archives of disease in childhood 67(1specno): 57-61	- Study does not include population of interest *[Babies with suspected early-onset infection]*
Solomon, R, Kuruvilla, K A, Job, V et al. (1999) Randomized controlled trial of once vs. twice daily gentamicin therapy in newborn. Indian pediatrics 36(2): 133-7	- Study does not include population of interest *[States babies in 'early neonatal life' but does not report age]*
Steele, R W and Bradsher, R W (1983) Comparison of ceftriaxone with standard therapy for bacterial meningitis. The Journal of pediatrics 103(1): 138-41	- Study does not include population of interest *[Includes neonates and children up to 14 years. Results for neonates not reported separately]*
Tessin, I, Thiringer, K, Trollfors, B et al. (1988) Comparison of serum concentrations of ceftazidime and tobramycin in newborn infants. European journal of pediatrics 147(4): 405-7	- Study does not include population of interest *[Study includes babies with suspected early-onset infection. Mean age is within the criteria for early-onset]*
Tessin, I, Trollfors, B, Bergmark, J et al. (1987) Enzymuria in neonates during treatment with gentamicin or tobramycin. Pediatric infectious disease journal 6(9): 870-871	- Study does not include population of interest *[One study arm only has babies with suspected early-onset infection]*

Study	Reason
Tessin, I, Trollfors, B, Thiringer, K et al. (1991) Ampicillin-aminoglycoside combinations as initial treatment for neonatal septicaemia or meningitis. A retrospective evaluation of 12 years' experience. Acta paediatrica Scandinavica 80(10): 911-6	- Not a relevant study design *[Non-comparative observational study]*
Tessin, I, Trollfors, B, Thiringer, K et al. (1989) Concentrations of ceftazidime, tobramycin and ampicillin in the cerebrospinal fluid of newborn infants. European journal of pediatrics 148(7): 679-81	- Study does not contain outcomes of interest *[Non-RCT which does not report antibiotic resistance outcomes]*
Tiwari, Soumya, Rehan, H S, Chandra, Jagdish et al. (2009) Efficacy and safety of a single daily dose of gentamicin in hospitalized Indian children: a quasi-randomized trial. The Journal of antimicrobial chemotherapy 64(5): 1096-101	- Study does not include population of interest *[Included neonates and children up to 11 years of age. Results not reported separately]*
Tullus, K and Burman, L G (1989) Ecological impact of ampicillin and cefuroxime in neonatal units. Lancet (London, England) 1(8652): 1405-7	- Study does not include population of interest *[No information about age of neonates]* - Study does not contain outcomes of interest *[Antibiotic resistance based on faecal culture]*
Umana, M A, Odio, C M, Castro, E et al. (1990) Evaluation of aztreonam and ampicillin vs. amikacin and ampicillin for treatment of neonatal bacterial infections. The Pediatric infectious disease journal 9(3): 175-80	- Study does not include population of interest *[Babies without proven infection excluded from analysis]*
Vergnano, Stefania, Menson, Esse, Kennea, Nigel et al. (2011) Neonatal infections in England: the NeonIN surveillance network. Archives of disease in childhood. Fetal and neonatal edition 96(1): f9-f14	- Not a relevant study design *[Non-comparative observational study]*
Violaris, Kimon, Carbone, Tracy, Bateman, David et al. (2010) Comparison of fluconazole and nystatin oral suspensions for prophylaxis of systemic fungal infection in very low birthweight infants. American journal of perinatology 27(1): 73-8	- RCT for antifungal treatment that does not meet the methods stated in the protocol *[Babies given antifungal treatment but no information about how many were also being given antibiotics]*
Vucicevic, K., Rakonjac, Z., Miljkovic, B. et al. (2014) Pharmacokinetic variability of amikacin	- Study does not contain outcomes of interest

Study	Reason
after once-daily and twice-daily dosing regimen in full-term neonates. Journal of Pharmacological Sciences 124(2): 138-143	
Vucicevic, K.M., Rakonjac, Z.M., Jankovic, B.Z. et al. (2014) Clinical pharmacokinetics in optimal gentamicin dosing regimen in neonates. Central European Journal of Medicine 9(3): 485-490	- Study does not contain outcomes of interest
Wainer, S., Cooper, P.A., Funk, E. et al. (1992) Prophylactic miconazole oral gel for the prevention of neonatal fungal rectal colonization and systemic infection. Pediatric Infectious Disease Journal 11(9): 713-716	- Study does not include population of interest *[Babies with suspected early-onset infection]*
Wiese, G (1988) Treatment of neonatal sepsis with ceftriaxone/gentamicin and with azlocillin/gentamicin: a clinical comparison of efficacy and tolerability. Chemotherapy 34(2): 158-63	- Study does not include population of interest *[States that neonates were included but no information about age]*
Zaidi, Anita K M, Tikmani, Shiyam Sundar, Sultana, Shazia et al. (2013) Simplified antibiotic regimens for the management of clinically diagnosed severe infections in newborns and young infants in first-level facilities in Karachi, Pakistan: study design for an outpatient randomized controlled equivalence trial. The Pediatric infectious disease journal 32suppl1: 19-25	- Community-based antibiotic regimes. Not relevant to UK practice
Zaidi, Anita K M, Tikmani, Shiyam Sundar, Warraich, Haider J et al. (2012) Community-based treatment of serious bacterial infections in newborns and young infants: a randomized controlled trial assessing three antibiotic regimens. The Pediatric infectious disease journal 31(7): 667-72	- Community-based antibiotic regimes. Not relevant to UK practice
Zeng, Zhangrui, Tian, Gang, Ding, Yinhuan et al. (2020) Epidemiology, antifungal susceptibility, risk factors and mortality of invasive candidiasis in neonates and children in a tertiary teaching hospital in Southwest China. Mycoses	- Study does not contain outcomes of interest *Observational study which does not report resistance outcomes*

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1 Economic studies

Study	Reason
Andrews RE. Audit of single daily dose gentamicin versus a variable frequency lower dose regimen in term and preterm neonates. BRITISH JOURNAL OF INTENSIVE CARE. 2000;10(2):42-6.	- Exclude overall. No health economic information relevant for this review question.
Blyth CC, Barzi F, Hale K, Isaacs D. Chemoprophylaxis of neonatal fungal infections in very low birthweight infants: efficacy and safety of fluconazole and nystatin. Journal of paediatrics and child health. 2012 Sep;48(9):846-51.	- Study is not an economic evaluation.
Chen S, Sun KY, Feng XW, Ran X, Lama J, Ran YP. Efficacy and safety of itraconazole use in infants. World Journal of Pediatrics. 2016 Nov 1;12(4):399-407.	- Exclude overall. No health economic information relevant for this review question.
De Cock RF, Smits A, Allegaert K, de Hoon J, Saegeman V, Danhof M, Knibbe CA. Population pharmacokinetic modelling of total and unbound cefazolin plasma concentrations as a guide for dosing in preterm and term neonates. Journal of Antimicrobial Chemotherapy. 2014 May 1;69(5):1330-8.	- Study is not an economic evaluation.
Gordon A, Jeffery HE. Antibiotic regimens for suspected late onset sepsis in newborn infants. Cochrane Database of Systematic Reviews. 2005(3).	- Study is not an economic evaluation
Ng TB, Cheung RC, Ye XJ, Fang EF, Chan YS, Pan WL, Dan XL, Yin CM, Lam SK, Lin P, Kui Ngai PH. Pharmacotherapy approaches to antifungal prophylaxis. Expert opinion on pharmacotherapy. 2012 Aug 1;13(12):1695-705.	- Exclude overall. No health economic information relevant for this review question.
Leonart LP, Tonin FS, Ferreira VL, da Silva Penteado ST, de Araújo Motta F, Pontarolo R. Fluconazole doses used for prophylaxis of invasive fungal infection in neonatal intensive care units: A network meta-analysis. The Journal of Pediatrics. 2017 Jun 1;185:129-35.	- Study is not an economic evaluation.
Mersal A, Alzahrani I, Azzouz M, Alsubhi A, Alsawaigh H, Albshri N, Bajammal M, Avand G, Almahbosh A. Oral nystatin versus intravenous fluconazole as neonatal antifungal prophylaxis:	- Study only contains costs.

Study	Reason
non-inferiority trial. Journal of clinical neonatology. 2013 Apr;2(2):88.	
Ramasamy S, Biswal N, Bethou A, Mathai B. Comparison of two empiric antibiotic regimen in late onset neonatal sepsis—a randomized controlled trial. Journal of tropical pediatrics. 2014 Feb 1;60(1):83-6.	- Study is not an economic evaluation
Reynolds LF, Mailman TL, McMillan DD. Gentamicin in neonates at risk for sepsis–peak serum concentrations are not necessary. Paediatrics & child health. 2012 Jun 1;17(6):310-2.	- Exclude overall. No health economic information relevant for this review question.
Swanson JR, Vergales J, Kaufman DA, Sinkin RA. Cost analysis of fluconazole prophylaxis for prevention of neonatal invasive candidiasis. The Pediatric Infectious Disease Journal. 2016 May 1;35(5):519-23.	- Though an economic evaluation comparing fluconazole prophylaxis vs no fluconazole prophylaxis, this study was excluded as it was not a CUA (no QALYs) and also because it had a different population (extremely low birthweight infants only).
Thureen PJ, Reiter PD, Gresores A, Stolpman NM, Kawato K, Hall DM. Once-versus twice-daily gentamicin dosing in neonates≥ 34 weeks' gestation: cost-effectiveness analyses. Pediatrics. 1999 Mar 1;103(3):594-8.	- Different decision problem. Not relevant to this review question.
Yang YC, Mao J. Value of platelet count in the early diagnosis of nosocomial invasive fungal infections in premature infants. Platelets. 2018 Jan 2;29(1):65-70.	- Study is not an economic evaluation.

1

Appendix K - Network meta-analysis results

Network meta-analyses were conducted for 3 outcomes in the review protocol for which data was available for 3 or more comparators: invasive fungal infection, mortality and length of stay. A binomial logit model was used for the invasive fungal infection and mortality outcomes as these are binary outcomes, and a normal identity model was used for the length of stay as this is a continuous outcome.

Model fit statistics for all outcomes

Studies which included fluconazole as one of the trial arms used a wide range of dose regimens, with some studies starting at lower doses and increasing the dosage over a range of time periods as well as differing doses in a final 'maintenance' period. In order to try to account for some of the heterogeneity caused by differing fluconazole doses, stratifying the studies by dose was investigated. Two strategies were investigated: splitting the data by average daily dose in the maintenance period (low dose <4 mg/kg/day vs high dose 4–6 mg/kg/day) and splitting treatments by total dose throughout the treatment period (low dose <70 mg/kg vs high dose >70 mg/kg), including any initial period where the full dose was not given. Accounting for dose in these ways did not substantially improve model fit (see details below) so models which assumed that the relative treatment effect did not depend on dose were preferred for all outcomes.

One RCT (Kaufman et al. 2005) compares 2 dosing schedules of fluconazole, both of which count as 'low daily dose', although 1 is 'low total dose' and the other is 'high total dose'. We have included these data in all 3 analyses, because although they contribute no information on the relative treatment effects, they do contribute to the estimation of between study variation and also make model fit metrics (DIC and deviance estimates) comparable between the different analyses. We also note that this trial found no difference in outcomes, lending support to our conclusion that different dosages may reasonably be pooled.

Model fit statistics

Number of Studies	Outcome	Model	Total residual deviance	Total model DIC	No. of data-points	Between-study SD (95% CrI)	Preferred model
Invasive fungal infection							
13	Invasive fungal infection (all fluconazole doses combined)	FE	42.5	154.3	28[a]	-	RE, combined dose[b]
		RE	28.4	146.9		0.75 (0.25, 1.60)	
13	Invasive fungal infection (fluconazole studies stratified by daily dose in maintenance period)	FE	41.1	153.9	28[a]	-	
		RE	28.7	147.7		0.75 (0.16, 1.72)	
13	Invasive fungal infection (fluconazole studies stratified by total dose in treatment period)	FE	43.0	155.8	28[a]	-	
		RE	28.6	147.9		0.81 (0.27, 1.78)	
Mortality							
14	Mortality (all fluconazole doses combined)	FE	33.8	174.6	32	-	FE, combined dose[c]
		RE	33.2	176.4		0.18 (0.01, 0.62)	
14	Mortality (fluconazole studies stratified by daily dose in maintenance period)	FE	33.9	175.7	32	-	
		RE	33.5	177.6		0.18 (0.01, 0.66)	
14	Mortality (fluconazole studies stratified by total dose in treatment period)	FE	33.2	174.9	32	-	
		RE	33.2	176.9		0.15 (0.01, 0.60)	
Length of stay							
5	Length of stay in hospital or on neonatal unit (all fluconazole doses combined)	FE	17.3	78.2	14	-	FE, combined dose[d]
		RE	13.9	77.9		3.78 (0.33, 12.65)	
5	Length of stay (fluconazole studies stratified by daily dose in maintenance period)	FE	17.6	79.8	14	-	
		RE	14.0	78.8		5.02 (0.44, 15.93)	
5	Length of stay (fluconazole studies stratified by total dose in treatment period)	FE	16.8	79.0	14	-	
		RE	13.9	78.6		4.39 (0.25, 15.44)	

(a) 13 trials, 2 with 3 arms. One included 2-arm trial (Mersal et al. 2013) had zero infection events in each arm and so was excluded from the dataset.

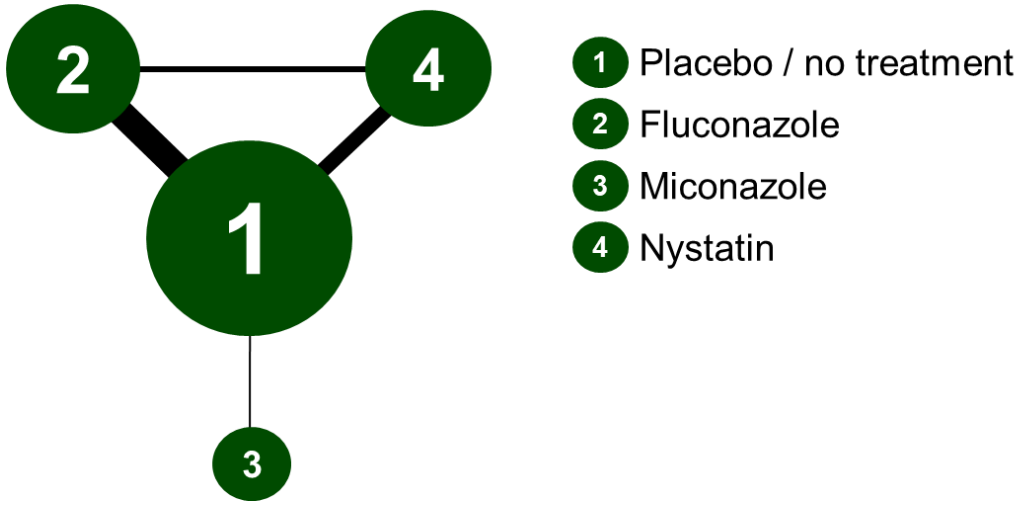
(b) Random effects model with doses combined was selected as the preferred model. Splitting treatments by daily dose in the maintenance period or total dose did not meaningfully reduce the between study standard deviation or the total residual deviance for random-effects models, and the fixed-effect models fitted poorly in all cases with the total residual deviance well in excess of the number of data points.

(c) The fixed-effect model with doses combined was selected as the preferred model. The random-effects model with doses combined had a similar total residual deviance and a larger DIC and so this model was not preferred over the fixed-effect model. Stratifying studies by daily dose in the maintenance period or total dose did not meaningfully reduce the total residual deviance or DIC.

(d) The fixed-effect model with doses combined was selected as the preferred model as the random-effects model did not have a DIC that was meaningfully lower (meaningful = difference in DIC of 3 points or more). Stratifying studies by daily dose in the maintenance period or total dose did not meaningfully reduce the total residual deviance or DIC.

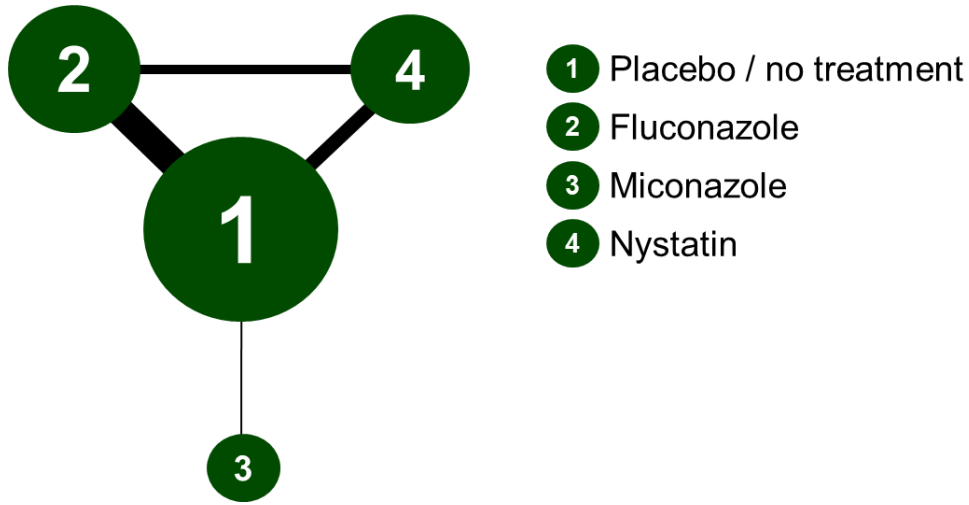
Network diagrams

Invasive fungal infection



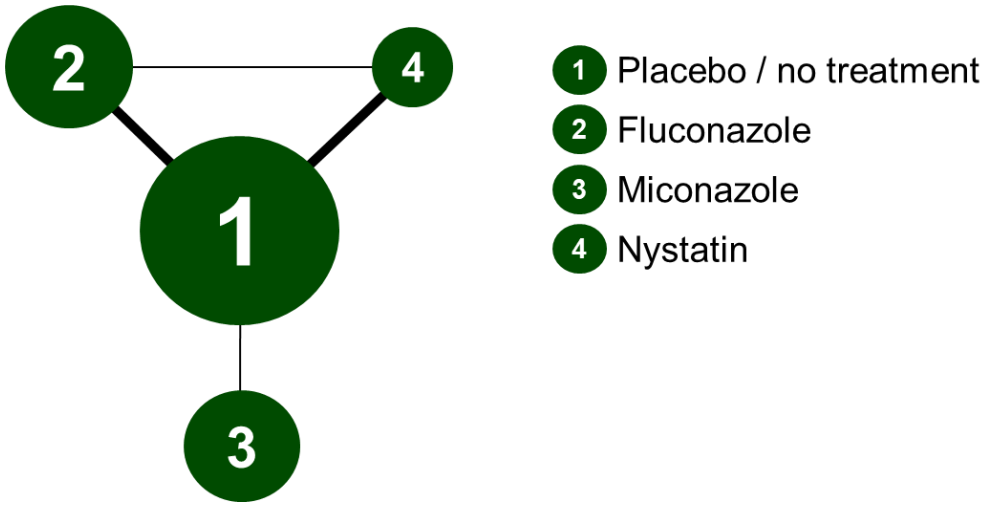
Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Mortality



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

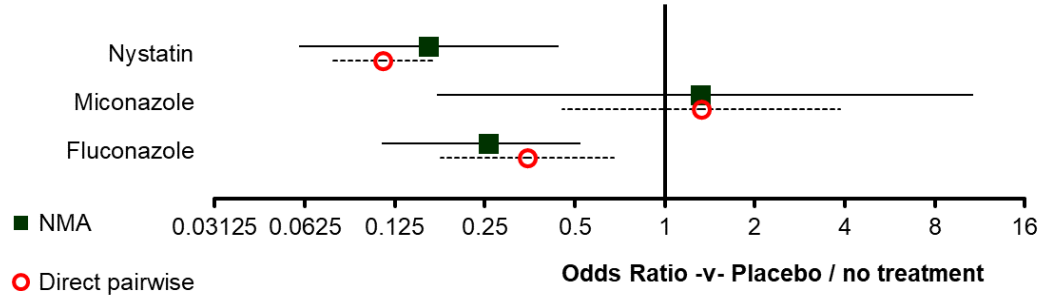
Length of stay



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

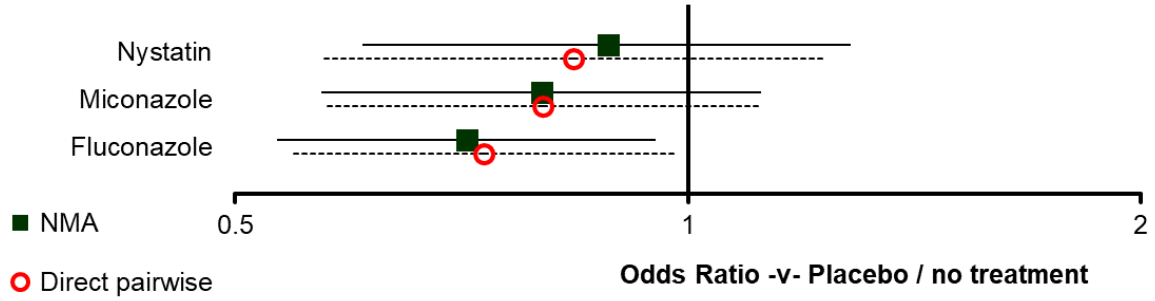
Caterpillar plots

Invasive fungal infection



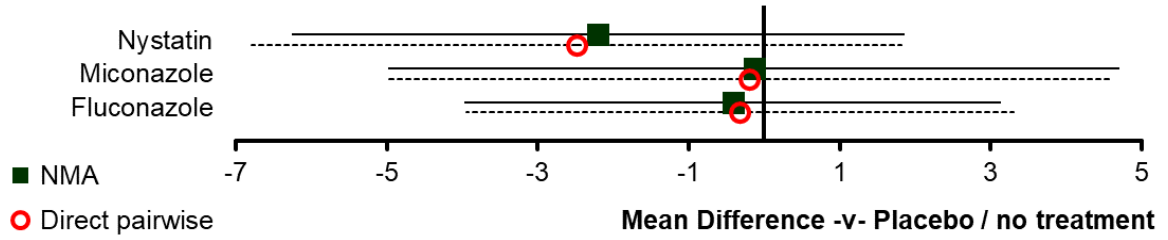
Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Mortality



Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

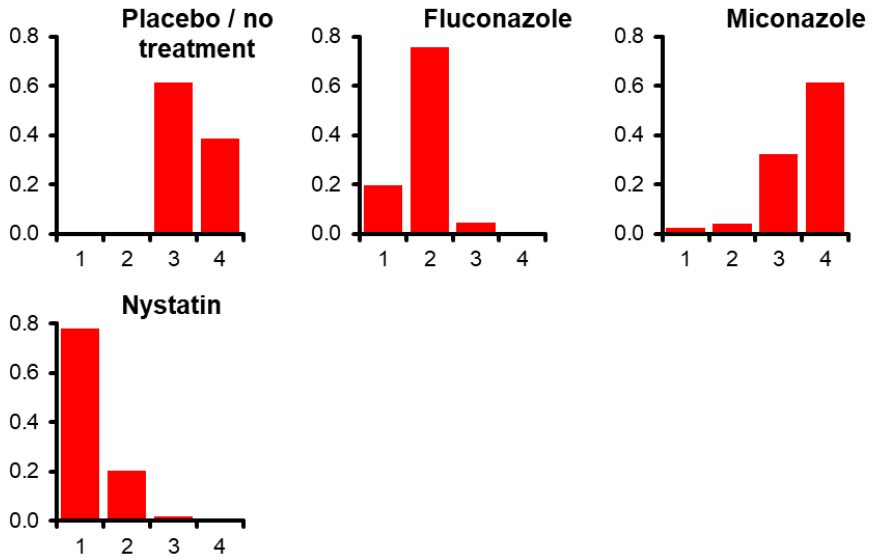
Length of stay



Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

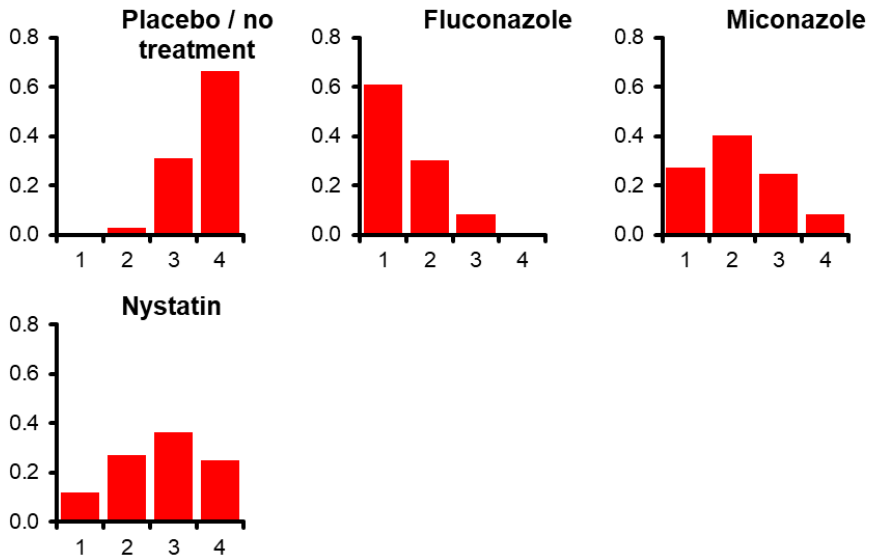
Rank probability histograms

Invasive fungal infection



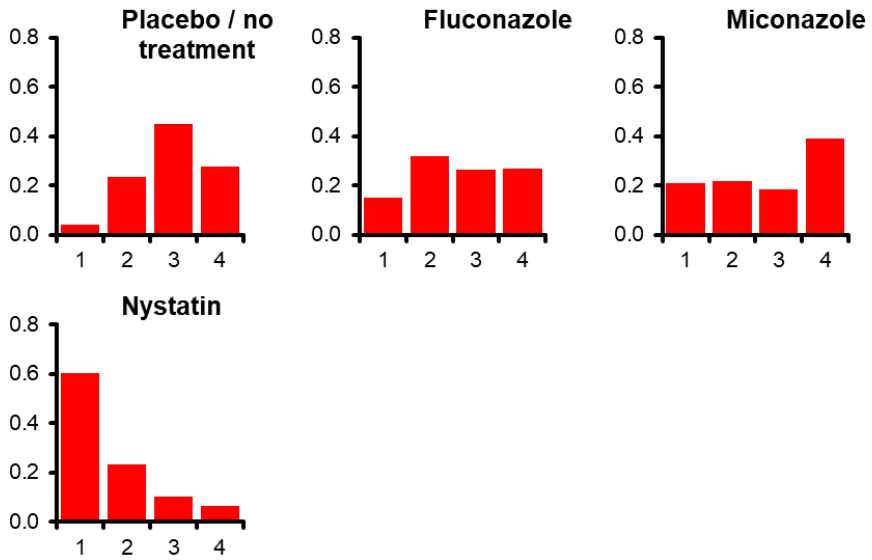
Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

Mortality



Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

Length of stay



Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

Relative effectiveness of pairwise combinations

Invasive fungal infection

Relative effectiveness of all pairwise combinations for invasive fungal infection. (Upper diagonal – Odds ratios (OR) with 95% confidence intervals from direct pair-wise meta-analysis. ORs less than 1 favour the column defining treatment. Lower diagonal – Posterior ORs with 95% credible intervals from NMA results. ORs less than 1 favour the row defining treatment.)

	Placebo / no treatment	Fluconazole	Miconazole	Nystatin
Placebo / no treatment		0.35 (0.18, 0.67)	1.32 (0.45, 3.86)	0.11 (0.08, 0.17)
Fluconazole	0.26 (0.11, 0.52)		-	1.93 (0.63, 5.94)
Miconazole	1.32 (0.17, 10.73)	5.18 (0.62, 50.27)		-
Nystatin	0.16 (0.06, 0.44)	0.63 (0.22, 2.11)	0.12 (0.01, 1.19)	

Values are odds ratios.
The lower diagonal segment of the chart is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects. The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals.
The upper diagonal segment of the chart gives pooled direct evidence (random-effects pairwise meta-analysis), where available. Numbers in parentheses are 95% confidence intervals. OR> 1 favours row-defining treatment

Mortality

Relative effectiveness of all pairwise combinations for mortality. (Upper diagonal – Odds ratios (OR) with 95% confidence intervals from direct pair-wise meta-analysis. ORs less than 1 favour the column defining treatment. Lower diagonal – Posterior ORs with 95% credible intervals from NMA results. ORs less than 1 favour the row defining treatment.)

	Placebo / no treatment	Fluconazole	Miconazole	Nystatin
Placebo / no treatment		0.73 (0.54, 0.98)	0.80 (0.57, 1.12)	0.84 (0.57, 1.23)
Fluconazole	0.71 (0.53, 0.95)		-	1.43 (0.63, 3.22)
Miconazole	0.80 (0.57, 1.12)	1.12 (0.72, 1.75)		-
Nystatin	0.88 (0.61, 1.28)	1.24 (0.79, 1.94)	1.11 (0.67, 1.83)	

	Placebo / no treatment	Fluconazole	Miconazole	Nystatin

Values are odds ratios.
The lower diagonal segment of the chart is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects. The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals.
The upper diagonal segment of the chart gives pooled direct evidence (random-effects pairwise meta-analysis), where available. Numbers in parentheses are 95% confidence intervals. OR> 1 favours row-defining treatment

Length of stay

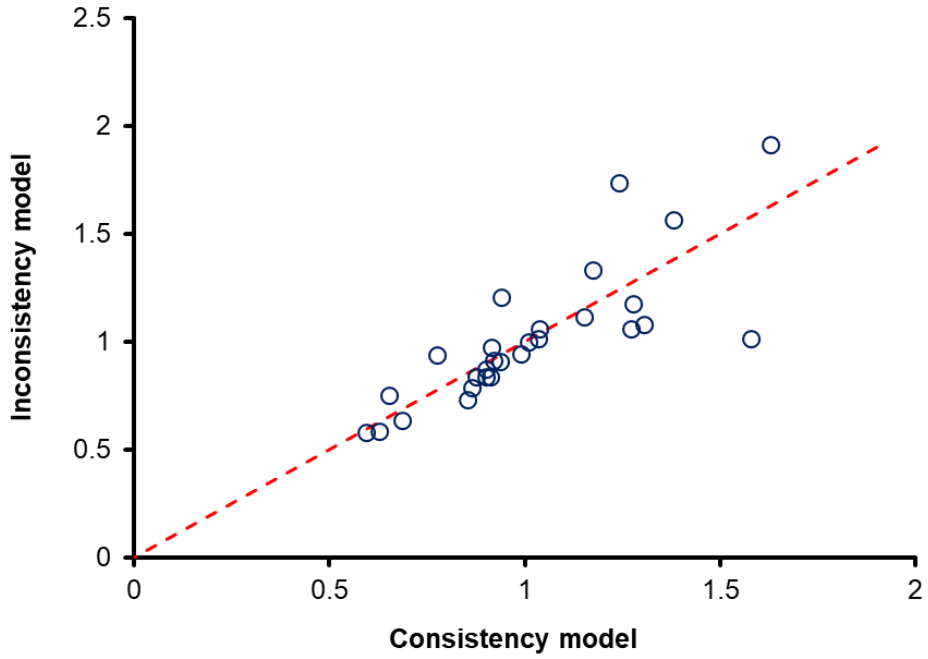
Relative effectiveness of all pairwise combinations for length of stay. (Upper diagonal – Odds ratios (OR) with 95% confidence intervals from direct pair-wise meta-analysis. MDs less than 0 favour the column defining treatment. Lower diagonal – Posterior MDs with 95% credible intervals from NMA results. MDs less than 0 favour the row defining treatment.)

	Placebo / no treatment	Fluconazole	Miconazole	Nystatin
Placebo / no treatment		-0.32 (-3.95, 3.30)	-0.20 (-4.96, 4.56)	-2.51 (-6.93, 1.90)
Fluconazole	-0.41 (-3.98, 3.14)		-	-1.00 (-7.34, 5.34)
Miconazole	-0.13 (-4.98, 4.70)	0.28 (-5.67, 6.29)		-
Nystatin	-2.21 (-6.27, 1.86)	-1.80 (-6.46, 2.87)	-2.06 (-8.33, 4.22)	

Values are mean differences in days.
The lower diagonal segment of the chart is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects. The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals.
The upper diagonal segment of the chart gives pooled direct evidence (random-effects pairwise meta-analysis), where available. Numbers in parentheses are 95% confidence intervals. MD> 0 favours row-defining treatment

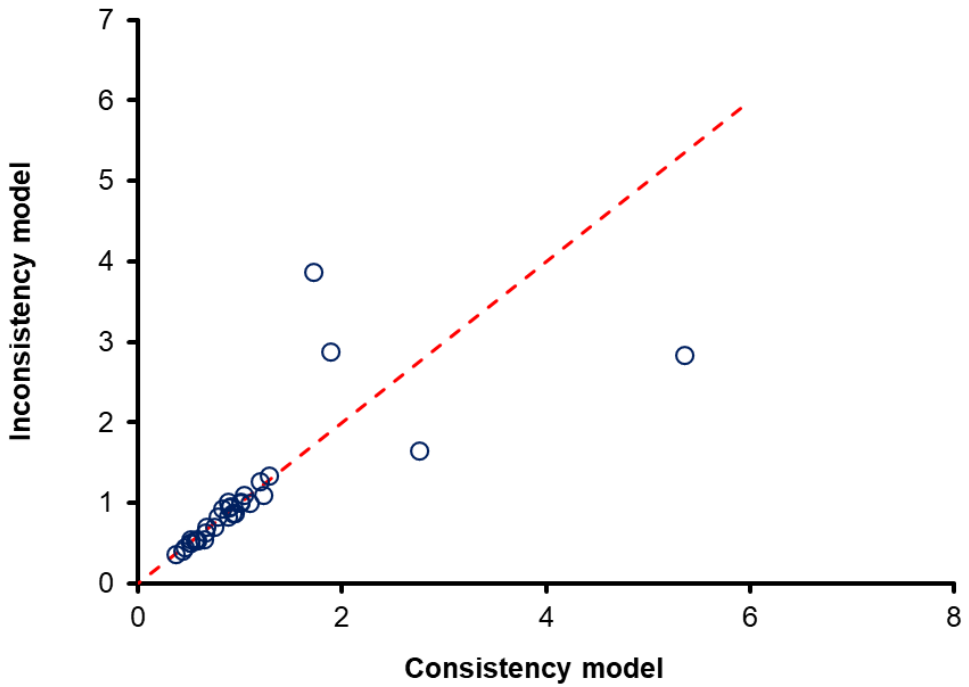
Inconsistency checking

Invasive fungal infection



Plot of the individual data points' posterior mean deviance contributions

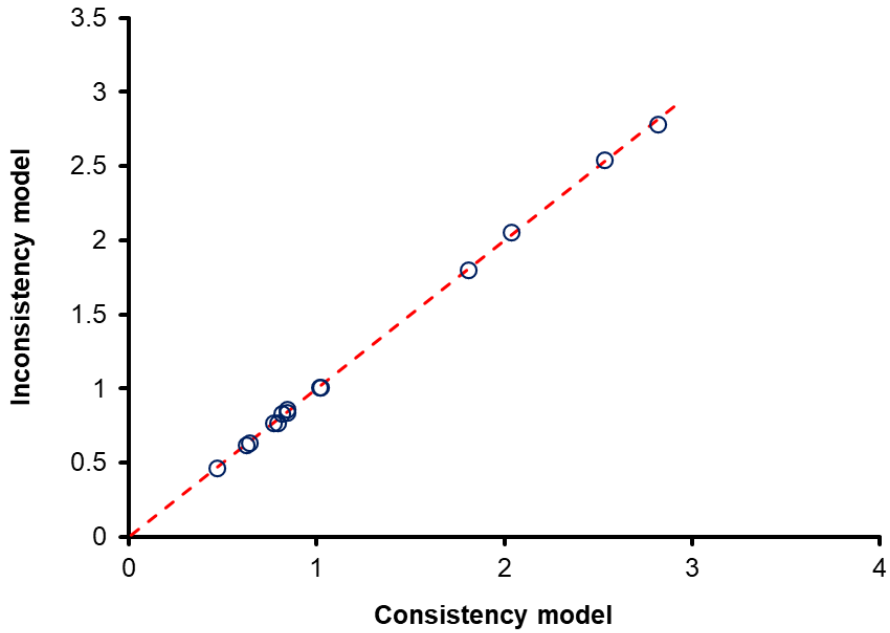
Mortality



Plot of the individual data points' posterior mean deviance contributions

The four outlying data points with high deviance contributions were investigated. These data points came from trials with zero events in one arm, which will always result in increased deviance. Therefore, these findings are not thought to indicate meaningful inconsistency.

Length of stay



Plot of the individual data points' posterior mean deviance contributions

Appendix L – WinBugs NMA code

The following code, using data from published NMAs in 2 systematic reviews, and additional data from studies published after the data of the systematic reviews, was used for the NMA.

Fixed-effect model for binomial data (logit link) – for odds ratios

```
# Binomial likelihood, logit link
# Fixed-effect model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                                # indexes studies
  mu[i] ~ dnorm(0, .0001)                               # vague priors for all trial
baselines
  for (j in 1:NumArms[i]) {                             # indexes arms
    k[i,j]        ~  dbin(p[i,j],N[i,j])              # binomial likelihood
    logit(p[i,j]) <- mu[i] + d[Rx[i,j]] - d[Rx[i,1]] # model for linear predictor
    rhat[i,j]     <- p[i,j] * N[i,j]                  # expected value of the numerators
    dev[i,j]      <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                     + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
                                                        # deviance contribution
    }                                                   # close arm loop
  resdev[i]     <- sum(dev[i,1:NumArms[i]])           # summed deviance contribution
  }                                                     # close study loop
totresdev     <- sum(resdev[])                          # total residual deviance

d[1]<-0                                                 # effect is 0 for reference
treatment
for (j in 2:NumRx) {                                    # indexes treatments
  d[j] ~ dnorm(0, .0001)                                # vague priors for treatment
effects
  }                                                     # close treatment loop

# Provide estimates of treatment effects T[j] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA

AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
for (j in 1:NumRx) {
  logit(Tmean[j]) <- AMean + d[j]
  logit(Tpred[j]) <- APred + d[j]
  }

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    lOR[c,j] <- (d[j]-d[c])
    OR[c,j]  <- exp(lOR[c,j])
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]     <- equals(rk[j],1)                        # probability that treat j is best
```

```
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                    # probability that treat j is hth
best
    }
  }
}
```

Random-effects model for binomial data (logit link) – for odds ratios

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                            # indexes studies
  mu[i] ~ dnorm(0, .0001)                           # vague priors for all trial
baselines
  delta[i,1] <- 0                                   # effect is zero for control arm
  w[i,1] <- 0                                       # multi-arm adjustment = zero for
ctrl
  for (j in 1:NumArms[i]) {                         # indexes arms
    k[i,j]        ~  dbin(p[i,j],N[i,j])            # binomial likelihood
    logit(p[i,j]) <- mu[i] + delta[i,j]             # model for linear predictor
    rhat[i,j]     <- p[i,j] * N[i,j]                # expected value of the numerators
    dev[i,j]      <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                     + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
                                                    # deviance contribution
    }                                               # close arm loop
  for (j in 2:NumArms[i]) {                         # indexes arms
    delta[i,j]  ~  dnorm(md[i,j],taud[i,j])         # trial-specific LOR distributions
    md[i,j]     <- d[Rx[i,j]] - d[Rx[i,1]] + sw[i,j] # mean of LOR distributions (with
multi-arm trial correction)
    taud[i,j]   <- tau *2*(j-1)/j                   # precision of LOR distributions
(with                                                      multi-arm trial correction)
    w[i,j]      <- (delta[i,j] - d[Rx[i,j]] + d[Rx[i,1]])
                                                    # adjustment for multi-arm RCTs
    sw[i,j]     <- sum(w[i,1:j-1])/(j-1)            # cumulative adjustment for multi-
arm                                                        trials
    }
  resdev[i]     <- sum(dev[i,1:NumArms[i]])         # summed deviance contribution
  }                                                 # close study loop
totresdev     <- sum(resdev[])                      # total residual deviance

d[1]<-0                                             # effect is 0 for reference
treatment
for (j in 2:NumRx) {                                # indexes treatments
  d[j] ~ dnorm(0, .0001)                            # vague priors for treatment
effects
  }                                                 # close treatment loop
sdu ~  dunif(RFXpriorParam1, RFXpriorParam2)        # uniform between-trial prior
sdn ~  dnorm(RFXpriorParam1, RFXpriorParam2)        # normal between-trial prior
sdl ~  dlnorm(RFXpriorParam1, RFXpriorParam2)       # lognormal between-trial prior
sd  <- sdu * equals(RFXpriorD,1) + sdn * equals(RFXpriorD,2) + sdl * equals(RFXpriorD,3)
                                                    # select correct between-trial
prior
tau <- pow(sd,-2)                                   # between-trial precision

# Provide estimates of treatment effects T[k] on the natural (probability) scale
AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
```

```
for (j in 1:NumRx) {
  logit(Tmean[j]) <- AMean + d[j]
  logit(Tpred[j]) <- APred + d[j]
  }

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    lOR[c,j] <- (d[j]-d[c])
    OR[c,j]  <- exp(d[j]-d[c])
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]     <- equals(rk[j],1)                    # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                    # probability that treat j is hth
best
    }
  }
}
```

Fixed-effects model for mean differences

```
# Normal likelihood, identity link
# Fixed-effect model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                            # indexes studies
  mu[i] ~ dnorm(0, .0001)                           # vague priors for all trial
baselines
  for (j in 1:NumArms[i]) {                         # indexes arms
    se[i,j]    <- SD[i,j] / sqrt(N[i,j])
    var[i,j]   <- pow(se[i,j],2)                    # calculate variances
    prec[i,j]  <- 1/var[i,j]                        # set precisions
    MC[i,j]    ~  dnorm(theta[i,j],prec[i,j])       # normal likelihood
    theta[i,j] <- mu[i] + d[Rx[i,j]] - d[Rx[i,1]]   # model for linear predictor
    dev[i,j]   <- (MC[i,j] - theta[i,j]) * (MC[i,j]
                  - theta[i,j]) * prec[i,j]         # deviance contribution
    }                                               # close arm loop
  resdev[i]    <- sum(dev[i,1:NumArms[i]])          # summed deviance contribution
  }                                                 # close study loop
totresdev      <- sum(resdev[])                     # total residual deviance

d[1]<-0                                             # effect is 0 for reference
treatment
for (j in 2:NumRx) {                                # indexes treatments
  d[j] ~ dnorm(0, .0001)                            # vague priors for treatment
effects
  }                                                 # close treatment loop

# Provide estimates of treatment effects T[j] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
```

```
for (j in 1:NumRx) {
  Tmean[j] <- AMean + d[j]
  Tpred[j] <- APred + d[j]
  }

# pairwise MDs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    MD[c,j] <- (d[j] - d[c])
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]     <- equals(rk[j],1)                    # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                    # probability that treat j is hth
best
    }
  }
}
```

Random-effects model for mean differences

```
# Normal likelihood, identity link
# Fixed effects model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                            # indexes studies
  w[i,1]       <- 0                                 # multi-arm adjustment = 0 for
control
  delta[i,1]   <- 0                                 # treatment effect is 0 for control
  mu[i]        ~  dnorm(0, .0001)                   # vague priors for all trial
baselines
  for (j in 1:NumArms[i]) {                         # indexes arms
    se[i,j]    <- SD[i,j] / sqrt(N[i,j])
    var[i,j]   <- pow(se[i,j],2)                    # calculate variances
    prec[i,j]  <- 1/var[i,j]                        # set precisions
    MC[i,j]    ~  dnorm(theta[i,j], prec[i,j])      # normal likelihood
    theta[i,j] <- mu[i] + delta[i,j]                # model for linear predictor
    dev[i,j]   <- (MC[i,j] - theta[i,j]) * (MC[i,j]
                  - theta[i,j]) * prec[i,j]         # deviance contribution
    dummy[i,j] <- ArmNo[i,j]                        # data not used in this model
    }                                               # close arm loop
  for (j in 2:NumArms[i]) {                         # indexes arms
    delta[i,j] ~  dnorm(md[i,j],taud[i,j])          # trial-specific MD distributions
    md[i,j]    <- d[Rx[i,j]] - d[Rx[i,1]] + sw[i,j]   # mean of MD dists, with multiarm
    taud[i,j]  <- tau *2*(j-1)/j                    # precision of MD dists, with
multiarm
    w[i,j]     <- (delta[i,j] - d[Rx[i,j]] + d[Rx[i,1]]) # adjustment, multi-arm RCTs
    sw[i,j]    <- sum(w[i,1:j-1])/(j-1)             # cumulative adjustment for multi-
arm
    }
  resdev[i]    <- sum(dev[i,1:NumArms[i]])          # summed deviance contribution
  dummy2[i]    <- Yrs[i] * RefID[i]                 # data not used in this model
  }                                                 # close study loop
```

```
totresdev      <- sum(resdev[])                       # total residual deviance

d[1]<-0                                               # effect is 0 for reference
treatment
for (j in 2:NumRx) {                                  # indexes treatments
  d[j] ~  dnorm(0, .0001)                             # vague priors for treatment
effects
  }                                                   # close treatment loop
sdu ~  dunif(RFXpriorParam1, RFXpriorParam2)          # uniform between-trial prior
sdn ~  dnorm(RFXpriorParam1, RFXpriorParam2)          # normal between-trial prior
sdl ~  dlnorm(RFXpriorParam1, RFXpriorParam2)         # lognormal between-trial prior
sd  <- sdu * equals(RFXpriorD,1) + sdn * equals(RFXpriorD,2) + sdl * equals(RFXpriorD,3)
tau  <- pow(sd,-2)                                    # between-trial precision

# Provide estimates of treatment effects T[j] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA

AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
for (j in 1:NumRx) {
  Tmean[j] <- AMean + d[j]
  Tpred[j] <- APred + d[j]
  }
dummy3        <- YrsA                                 # data not used in this model

# pairwise MDs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    MD[c,j] <- (d[j] - d[c])
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]     <- equals(rk[j],1)                      # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                      # probability that treat j is hth
best
    }
  }
}
```

Inconsistency models

The examples given here are for binomial data with a logit link; other likelihoods and link functions were the same as those given above.

Fixed-effect

```
model {
for(i in 1:NumStudies) {
  mu[i] ~ dnorm(0, .0001)                          # vague priors for trial baselines
  for (j in 1:NumArms[i]) {                        # indexes arms
    k[i,j]        ~  dbin(p[i,j], N[i,j])          # binomial likelihood
    logit(p[i,j]) <- mu[i] + d[Rx[i,1],Rx[i,j]]    # model for linear predictor
    rhat[i,j]     <- p[i,j] * N[i,j]               # expected value of numerators
    dev[i,j]      <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                     + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
```

```
                                                    # deviance contribution
    }                                               # close arm loop
  resdev[i]     <- sum(dev[i,1:NumArms[i]])         # summed deviance contribution
  }
totresdev <- sum(resdev[])                          # total residual deviance
for (j in 1:NumRx) {
  d[j,j] <- 0                                       # effect=0 for j vs j
  }
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    d[c,j]  ~  dnorm(0, .0001)
              OR[c,j] <- exp(d[c,j])
    }
  }
dummy3 <- meanA + precA + predA + predPrecA + YrsA + blnHiGood # not used in this model
}
```

Random effects

```
model {
for(i in 1:NumStudies) {
  mu[i]      ~  dnorm(0, .0001)                    # vague priors for trial baselines
  delta[i,1] <- 0                                  # treatment effect is zero in control
arm
  for (j in 2:NumArms[i]) {
    delta[i,j] ~  dnorm(d[Rx[i,1],Rx[i,j]], tau)  # trial-specific LOR distributions
  }
  for (j in 1:NumArms[i]) {
    k[i,j]        ~  dbin(p[i,j], N[i,j])         # binomial likelihood
    logit(p[i,j]) <- mu[i] + delta[i,j]           # model for linear predictor
    rhat[i,j]     <- p[i,j] * N[i,j]              # expected value of numerators
    dev[i,j]      <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                     + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
                                                  # deviance contribution
    }
  resdev[i]     <- sum(dev[i,1:NumArms[i]])       # summed residual deviance
contribution
  }
totresdev <- sum(resdev[])                        # total residual deviance
for (j in 1:NumRx) {
  d[j,j] <- 0                                     # effect=0 for j vs j
  }
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    d[c,j]  ~  dnorm(0, .0001)
              OR[c,j] <- exp(d[c,j])
    }
  }
sdu ~  dunif(RFXpriorParam1, RFXpriorParam2)      # uniform between-trial prior
sdn ~  dnorm(RFXpriorParam1, RFXpriorParam2)      # normal between-trial prior
sdl ~  dlnorm(RFXpriorParam1, RFXpriorParam2)     # lognormal between-trial prior
sd  <- sdu * equals(RFXpriorD,1) + sdn * equals(RFXpriorD,2) + sdl * equals(RFXpriorD,3)
                                                  # select correct between-trial prior
tau <- pow(sd,-2)                                 # between-trial precision
dummy3 <- meanA + precA + predA + predPrecA + YrsA + blnHiGood
                                                  # not used in this model
}
```