National Institute for Health and Care Excellence

Draft

Neonatal infection: antibiotics for prevention and treatment

[C] Evidence review for timing of delivery to reduce the risk of early-onset neonatal infection

NICE guideline <number>

Evidence reviews underpinning recommendation 1.2.9 and research recommendations in the NICE guideline

December 2020

Draft for Consultation

These evidence reviews were developed by NICE Guideline Updates Team

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Timing of delivery for women with preterm prelabour prolonged rupture of membranes and group B streptococcus

1.1 Review question

What is the clinical and cost effectiveness of immediate delivery versus expectant management for women between 34- and 37-weeks' gestation with preterm prelabour prolonged rupture of membranes and vaginal or urine group B streptococcus detection during the current pregnancy to reduce the risk of neonatal infection?

1.1.1 Introduction

Neonatal infection is a significant cause of mortality and morbidity in neonates. It can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths. Early-onset neonatal infection is less common than late-onset neonatal infection, but it is often more severe. It is present in 1 of every 1000 newborn babies and responsible for 9 of every 1000 neonatal admissions. Group B streptococcus (GBS) and Escherichia coli are the most common organisms identified. Overall mortality is reported to be about 10% but is even higher in preterm babies. Up to 7% of babies who survive GBS infection have a consequent disability.

Preterm prelabour rupture of membranes (PPROM) is the rupture of membranes before the onset of labour in women who are at less than 37 weeks gestation. PPROM can be managed either by immediate delivery via induction of labour or caesarean section, or by expectant management, where women are closely monitored until either spontaneous labour, deferred induction of labour or caesarean section. The NICE guideline on intrapartum care makes recommendations on management of rupture of membranes at term but this does not include women who experience rupture of membranes pre-term. The aim of this review is to compare the clinical and cost-effectiveness of immediate delivery and expectant management for women who have GBS during the current pregnancy and experience PPROM between 34+0 and 37+6 weeks gestational age.

1.1.2 Summary of the protocol

Table 1: PICO table

Population	Women with preterm prelabour prolonged rupture of membranes between 34+0 and 37+6 weeks gestation with urine or vaginal GBS detected during current pregnancy
Interventions	Induction of labour
Comparator	Expectant management
Outcomes	• Culture-proven infection from sample taken from the neonate within 72 hours of birth where available or within the study-defined period for early-onset neonatal infection. • suspected bloodstream infection (in neonate) based on clinical symptoms within 72 hours of birth where available or within the study-defined period for early-onset neonatal infection. • Neonatal mortality (at different time points – peri-natal mortality (stillborn or within 7 days from birth) or greater than 7 days from birth)

- health-related quality of life of neonate, measured using a validated tool
- hospital length of stay (maternal)
- hospital length of stay (neonatal)
- psychological distress in baby's family as measured using a validated scale (e.g. parental stressor scale NICU; modified Rutter Malaise Inventory)
- evidence of maternal sepsis (including maternal antibiotic administration)
- neonatal respiratory distress syndrome
- number of caesarean sections

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 details of the 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. The review protocol specified that, where possible, subgroup analyses would be conducted for vulnerable women, including women who were non-attenders at neonatal clinics, women with low socio-economic status, women with low incomes or level of education.

This review did not use the GRADE imprecision parameter as part of the quality assessment of outcome measures. Where the interpretation of the effect is stated in the quality assessment table (Table 3), an outcome was reported as "could not differentiate" between trial arms when the confidence (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

The initial search returned a total of 457 results. Of these, 23 were identified as potential included studies and full text articles were ordered and reviewed against the inclusion criteria. Two RCTs met the inclusion criteria and were included within the review.

The search was re-run in July 2020 to identify any studies which had been published since the date of the original search. This returned a total of 41 results of which 3 were identified as possible included studies. After full text review, 0 met the inclusion criteria. In total there were therefore 2 studies (both RCTs) which met the inclusion criteria for this review.

1.1.4.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of included clinical studies

Study	Study type and follow-up time	Population	Intervention (expectant management)	Comparator (immediate delivery)	Outcomes
Morris 2016 (subgroup of PPROMT trial – women with GBS) (trial n=1839, subgroup n=171)	• RCT • 28 day follow-up	• Women between 34- and 36- weeks gestation with PPROM and a singleton pregnancy • Women with ruptured membranes prior to 34 weeks included if their latency period extended to 34 weeks	Birth after spontaneous labour at term or when the clinician felt necessary based on clinical symptoms	As close to randomisation as possible, preferably within 24 hours	• Neonatal sepsis *(definite or possible neonatal infection)*
Tajik 2014 (Post-hoc analysis of PPROMEXIL trial – subgroup of women with GBS) (trial n=776, subgroup n=103)	• RCT • Follow-up 72 hours after birth	• Women with a singleton or twin pregnancy • Women presenting with PPROM between 34+0 and 36+6 weeks of gestation and not in labour within 24 hours of membrane rupture • Women with PPROM after 26+0 weeks gestation who had	Expectant management *(monitored until spontaneous delivery or until 37+0 weeks when labour was induced)*	Immediate delivery *(induced within 24 hours of randomisation)*	• Early-onset neonatal infection *(proven or suspected neonatal infection within 72 hours of birth)* • Neonatal length of stay • Neonatal respiratory distress syndrome • Number of caesarean sections

Study	Study type and follow-up time	Population	Intervention (expectant management)	Comparator (immediate delivery)	Outcomes
		not delivered by 34+0 weeks			

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3. Quality assessment of clinical studies included in the evidence review

Outcome	No. studies	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Early-onset neonatal infection (confirmed or suspected)	1 (Tajik 2014)	103	RR 8.67 (1.11 to 67.98)	Moderate	Favours immediate delivery
Neonatal sepsis (early- or late-onset not specified)	1 (Morris 2016)	171	RR 1.06 (0.22 to 5.11)	Low	Could not differentiate
Neonatal infection (early-onset neonatal infection and neonatal sepsis)	2 (Morris 2016, Tajik, 2014)	274	RR 2.73 (0.34, 22.18)	Very low	Could not differentiate
Neonatal length of stay (days)	1 (Tajik 2014)	103	MD -1.50 (-3.70 to 0.70)	Moderate	Could not differentiate
Neonatal respiratory distress syndrome	1 (Tajik 2014)	103	RR 0.50 (0.10 to 2.44)	Moderate	Could not differentiate
Number of women given caesarean section	1 (Tajik 2014)	103	RR 0.79 (0.33 to 1.87)	Moderate	Could not differentiate

See appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see **Error! Reference source not found.**). This search retrieved 4,398 studies.Based on titles and abstracts screening, 10 studies were suspected to be relevant, of which 9 were excluded and only 1 study was ultimately included.

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. In total there was therefore 1 published study which met the inclusion criteria for this review.

1.1.7.2 Excluded studies

See Appendix J for list of excluded studies.

1.1.8 Summary of included economic evidence

Table 4 provides summary details of the included study. See appendix I for a full evidence table and assessment of applicability and limitations.

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

1.1.9 Economic model

Table 4: Summary of economic evidence

Applicability & limitations	Methods	Intervention	Absolute		Incremental			Uncertainty
			Cost (£)	Effects	Cost (£) (95% CI)	Effects (95% CI)	ICER	
Lain et al. (2017)								
Partially applicable with **serious limitations**	Cost-effectiveness study performed alongside randomised trial (PPROMT). **Effects:** 1) Neonatal sepsis (anytime before infants discharged); 2) Neonatal respiratory distress syndrome (NRDS). **Costs:** Within-RCT resource-use (antenatal care, delivery, postnatal length of stay). Unit costs from NHS RefCosts (UK) **Utility:** Not a cost–utility analysis.	**Outcome: sepsis**						**Deterministic:** analysis using UK-only resource-use data produced relatively similar – though more uncertain – estimate of difference in total costs (308 [−801 to 1530]). **Probabilistic:** Bootstrap using 5,000 resamples to estimate 95% CI.
		Expectant	–	–				
		Immediate	–	–	£112 (−£431, £662)	−0.007 (−0.02, 0.01)	£16,000 per sepsis prevented	
		Outcome: RDS						
		Expectant	–	–				
		Immediate	–	–	as above	0.03 (0.01, 0.06)	Dominated	
Original model developed for this guideline (see appendix I)								
Directly applicable with **minor limitations**	3 linked decision-trees (infections; RDS; mode of delivery); lifetime consequences **Effects:** Systematic review of RCTs as reported in this review **Costs:** Resource-use from Lain et al. (2017) and Schroeder et al. (2009). Long-term morbidity from Petrou et al. (2013). Unit cost from NHS RefCosts (UK) **Utilities:** Long-term morbidity from Petrou et al. (2013).	**Outcome: QALYs**						**Deterministic:** Only parameter with a material effect on results is odds ratio for probability of infection (95%CI encompasses harm as well as benefit for immediate delivery). Immediate delivery will be preferred if OR >1.015 **Probabilistic:** c82% probability that immediate delivery is optimal, regardless of value placed on QALYs.
		Immediate	£14,372	24.705				
		Expectant	£19,311	24.371	£4,939	-0.333	Dominated	

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1 The outcomes that matter most

The committee stated that both maternal and neonatal outcomes were important when considering management options for women with prolonged premature rupture of membranes (PPROM). However, there was limited information on maternal outcomes, where the only evidence was for the number of women given caesarean sections. For outcomes in the baby, the committee were interested in the number of babies who developed neonatal infection, as this can lead to death, or short- and long-term complications and disability. It was also interested in other potential harms, such as respiratory distress syndrome. Length of stay was also considered important as this can impact on both the baby and their family, as well as resulting in additional costs for the NHS. Information was available for all these outcomes to help inform committee discussions.

1.1.10.2 The quality of the evidence

There was limited evidence available for this review, with only two studies meeting the inclusion criteria. One study (Morris 2016) was partially applicable to the research question as not all women included in the study met the definition for PPROM, with some having latency periods between rupture of membranes and birth of less than 24 hours. However, with the limited evidence base, the committee decided that the results should still be included in the analyses. To reflect the difference in population between the study and the research question, the quality of the study outcomes were downgraded for indirectness. Tajik (2001) was a post-hoc subgroup analysis of a larger study comparing immediate delivery with expectant management for women with prolonged prelabour rupture of membranes between 34- and 37-weeks' gestation irrespective of Group B streptococcus test status.

Evidence was only available for a small number of the outcomes stated in the protocol, and there was very limited information for maternal outcomes. Outcomes were very low- to moderate-quality primarily because all results were based on subgroups of women with GBS from the original trials, with limited information about the participants included in the subgroups and how the results were analysed. With the exception of neonatal infection, outcomes were based on the results of a single study rather than pooled meta-analysis.

The committee highlighted that the difference between mean gestational age of the babies in each arm of the studies was only a few days. In practice, the difference in gestational age between a baby who is born following immediate delivery or expectant management may be much greater. The short time period between immediate delivery and expectant management seen in the studies mean that differences in outcomes between the two study arms may therefore be from other factors as well as timing of delivery. The committee did not think this was enough to downgrade the studies for indirectness, but this was something that it considered when discussing the results. The committee felt that it was possible to make a recommendation based on a combination of this evidence and its clinical knowledge and experience.

1.1.10.3 Imprecision and clinical importance of effects

Neonatal infections were lower in the immediate delivery group compared with expectant management. When the 2 included studies were meta-analysed, this effect had a high degree of imprecision, and was non-significant, with confidence intervals crossing the line of no effect. When the study that was only partially applicable (because not all women had prolonged rupture of membranes) was removed from the analysis, the size of the effect was much larger, and was statistically significant. There was less imprecision in the results, and

the confidence intervals did not cross the line of no effect. The committee agreed that the point estimate for both the meta-analysed result and the result with the partially applicable study removed represented clinically very important effects as neonatal infection is such a serious outcome.

Rates of respiratory distress syndrome were lower in the expectant management group than the immediate delivery group, favouring expectant management. This was consistent with the knowledge and experience of the committee, as respiratory distress syndrome is associated with prematurity, and the babies in the expectant management group were delivered at a later gestation, on average. However, the confidence intervals surrounding this effect estimate showed a lot of imprecision because of the small sample size in the single study reporting this outcome, and the confidence intervals crossed the line of no effect. The committee noted however that the point estimate was very similar to the point estimate for respiratory distress syndrome in the larger trial from which this subgroup was reported, and in the larger trial the confidence intervals were narrower and did not cross the line of no effect. As such, they thought that the effect estimate was likely to reflect a clinically important effect in the GBS subgroup. However, it was also discussed how the short- and long-term impacts of a baby developing neonatal infection tend to be more severe than the effects of respiratory distress syndrome. The infection outcome was therefore considered most important, and recommendations were made in favour of immediate delivery over expectant management

Caesarean-section rate and length of stay were also lower in the expectant management group than the immediate delivery group, although these effects also had a high degree of imprecision, with confidence intervals that crossed the line of no effect. The committee agreed that the differences would be clinically important if the point estimates represented the true effect. However, without further research that would potentially reduce the imprecision for these outcomes, it could not be certain of the true effects of each method of delivery on these outcomes. Decisions on the recommendations were therefore based on the results of the neonatal infection outcomes and results of the health economic modelling.

The effects of imprecision on the certainty the committee could have in the results was explored further using economic modelling (described in the section on cost effectiveness and resource use).

1.1.10.4 Benefits and harms

The evidence suggested that immediate delivery may reduce the number of babies who need to be treated for neonatal infection. Reducing the number of babies treated for infection can improve outcomes for both the baby and their family, as well as reducing the associated costs of treatment and length of stay in hospital. The consequences of neonatal infection are very serious and can include death or long-term disability.

The committee were aware that earlier delivery could be associated with an increased risk of respiratory distress syndrome, more caesarean sections and a longer length of stay in a neonatal unit. However , the committee discussed how an increased risk of respiratory distress syndrome is a lower risk to the baby than those associated with neonatal infection. Respiratory distress syndrome is usually treatable and not associated with long-term morbidity. Caesarean sections can have consequences for future pregnancies, resulting in a small increase in the risk of still birth, ectopic pregnancy and miscarriage, and also making a future caesarean section more likely. However, as discussed above in the section on imprecision, the evidence was very uncertain because of the small number of women included in the analysis and the wide confidence intervals which crossed the line of no effect.

Because of the trade-off between benefits and harms as well as the uncertainty in the evidence, the committee decided that it would be useful to weigh up the consequences of

immediate delivery and expectant management in a decision model. This is described in the section on cost effectiveness and resource use below.

1.1.10.5 Cost effectiveness and resource use

The committee reviewed economic evidence on the cost effectiveness of immediate delivery versus expectant management, both from existing literature and from the economic model developed for this guideline. The evidence from the literature came from 1 cost-effectiveness analysis that had several limitations. First, UK participants only composed a portion of the participants in the study (22%) and, while country specific results were given, by excluding the other countries the sample size decreases and with it our certainty in the results. Second, GBS-colonised women composed a small portion of the study participants (9%), decreasing this study's applicability to the decision-problem for this review. Finally, this study only evaluated the immediate costs for each option and did not evaluate long term impacts on health and NHS costs. The committee therefore prioritised this question in the health economic plan so that an original cost per quality adjusted life year (QALY) model could be developed to overcome these limitations.

The committee viewed the primary problem for the model to address as a trade-off between the problems with prematurity associated with immediate delivery versus a risk of increased neonatal infection due to prolonging pregnancy. Additionally, the committee wanted the model to account for differences in mode of delivery (especially the proportion of caesarean sections), as these are a possible consequence of this decision. This has implications not only for short-term costs but also for long-term effects on future pregnancies: women with a history of caesarean section are known to be at somewhat greater risk for adverse outcomes including miscarriage, ectopic pregnancy and stillbirth.

The committee discussed the economic evidence from the de novo model. In the model's base case, immediate delivery dominates expectant management, meaning immediate delivery is both less costly and results in more QALYs. This is largely because the model suggests that, when compared with the outcomes that are more common with immediate delivery (RDS, need for caesarean section), the outcomes that are more common with expectant management (infection) are more expensive to treat and have a much greater impact on mortality and morbidity.

The committee saw that, in deterministic sensitivity analysis, immediate delivery remains the optimal option when all except 1 of the model's input parameters are varied within the range of their uncertainty. The odds ratio of infection is the single parameter that can be changed such that expectant management is favoured. This shows that the results of the model are almost entirely determined by which strategy is more successful in avoiding cases of neonatal infection. Probabilistic sensitivity analysis also favoured immediate delivery, with that approach providing the best balance of costs and benefits in around 85% of model iterations. The outputs of the probabilistic analysis also provided further support that the odds ratio of infection is the parameter largely determining the model results (because there are no iterations in which either approach is associated with higher costs and better outcomes: the option with the lowest infection-rate is both cheaper and more effective in all cases).

Due to the model's sensitivity to the strategy that most effectively reduces infections, the committee discussed the relative effectiveness evidence used in the model, which comes from 2 pooled RCTs: OR = 2.93 (95%CI: 0.33 to 26.19). It noted that, while the point estimate of this odds ratio favours immediate delivery quite strongly, at a 95% confidence level, the data are also consistent with a lower incidence of infections with expectant management. However, it also noted that the 1 study that precisely matches the decision problem (that is, only recruiting women with prolonged [>24hr] rupture of membranes; Tajik et al. 2014), does in fact show a significant reduction in infections with immediate delivery.

Moreover, regardless of any statistical uncertainty about which approach results in fewer infections, the committee did not see any plausible mechanism by which immediate delivery increases risk of infection, whereas this is an obvious danger with expectant management. This is because, if a woman with ruptured membranes is colonised with GBS, the baby continues to be in an environment in which both the pathogen and a portal for transmission are present, but this is not the case with immediate delivery. Therefore, the committee agreed that infections must, to some degree, be more common with expectant management compared with immediate delivery. While we are uncertain about the magnitude of this effect, the results of the model show the odds of infection only have to be 1.5% higher with expectant management for immediate delivery to be the preferred strategy. The committee was confident that there must be at least this much of an effect.

In view of these considerations, the committee was confident in making a strong recommendation for immediate delivery be offered to women with preterm prelabour prolonged rupture of membranes and vaginal or urine GBS colonisation to reduce the risk of neonatal infection.

The committee considered the potential resource impact of its recommendation. Given that the RCOG's current 'green-top' guideline (GTG36) also encourages expedited delivery in this population, it is likely that most units already follow the approach the committee recommends. In any case, the committee did not believe that any increase in immediate deliveries would have an impact on overall resource-use because, while the delivery itself is associated with nominally greater costs, this is offset by greater savings in antenatal care. Furthermore, the model shows a significant downstream reduction in costs due to prevented infections that far outweighs any of the other areas where immediate delivery may increase costs.

The committee noted that, because (a) the model strongly favours immediate delivery for women with GBS detection and PPROM and (b) GBS tests are relatively inexpensive and accurate, it would almost certainly be an effective use of NHS resources to test women with PPROM at 34^{+0}–37^{+6} weeks' gestation for GBS, if their status is not already known. The benefits shown in this analysis would be enough to justify this, even without accounting for the benefit of intrapartum antibiotics in cases of what would otherwise be occult GBS. It noted that antenatal screening for GBS is not currently recommended in the UK, although ad hoc testing is variably undertaken in the NHS. However, this decision-point is beyond the scope of the current review.

The committee also noted that the RCOG's current 'green-top' guideline (GTG36) encourages expedited delivery in women with PPROM and evidence of colonisation in previous pregnancies (not only the current one). Again, the model developed for this guideline implies that this is likely to be sensible, as it shows that immediate delivery remains preferable to expectant management even when the absolute risk of GBS disease is low. Once more, however, the committee was unable to make a recommendation for these women as they are not included in the population for this review.

1.1.10.6 Other factors the committee took into account

The committee discussed the importance of patient information and choice when considering different management options and making women aware of both potential benefits and harms. As such, it was agreed that the women who have PPROM and a positive GBS test should be made aware of the options available to them. The importance of clinicians offering the mother the choice of immediate delivery, rather than making the choice themselves, was therefore emphasised.

It was also discussed how many women will be unaware of their GBS status as this is not routinely screened or tested for in the UK, although some hospitals undertake GBS testing

for women with prelabour rupture of membranes to aid decision making. Women who are unaware of their GBS status may not benefit from this recommendation. This could be a source of inequality because women with lower socioeconomic status might be less likely to access private GBS testing. The committee stated that it was difficult to overcome this discrepancy unless GBS testing becomes more routine, but this was beyond the scope of the current guideline. However, as the choice between immediate delivery and expectant management should be made between the patient and the clinician, these women will still be able to choose immediate delivery if they decide this is the best option.

The committee noted that immediate delivery could be either induction of labour or caesarean section, as neither study restricted the immediate delivery arm to induction. This reflects what happens in clinical practice and so the committee did not think that this should impact on the recommendations. Expectant management could refer to either deferred induction of labour, caesarean section or spontaneous labour.

The committee expressed disappointment that there were no data available to the economic model with which to estimate the health impacts on carers and family members when a baby who has neonatal infection dies or survives, either with or without disability. As such, committee members felt that the model may not fully capture some of the wider impacts of infection. However, the committee understood that, even if this were accounted for in the model, it would not materially influence results. This is because the uncertainty in model outputs overwhelmingly results from imprecision in the likelihood of infection, not in the impact of any events that transpire (in other words, additional information about the full impact of infections would widen the spread of outputs, but they would still centre around the same point of equilibrium). Nevertheless, the committee agreed that the face validity of future analyses would be improved by being able to account for the full impact of infections. Therefore, it put forth a research recommendation to assess the impacts on health-related quality of life for carers and family members in cases of neonatal death or survival, with or without long-term morbidity (Appendix K).

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendation 1.2.9 and the research recommendation on the impact of neonatal infection on quality of life of the baby's family.

1.1.12 References – included studies

1.1.12.1 Effectiveness

Morris, Jonathan M, Roberts, Christine L, Bowen, Jennifer R et al. (2016) Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPROMT trial): a randomised controlled trial. Lancet (London, England) 387(10017): 444-52

Tajik, P, van der Ham, D P, Zafarmand, M H et al. (2014) Using vaginal Group B Streptococcus colonisation in women with preterm premature rupture of membranes to guide the decision for immediate delivery: a secondary analysis of the PPROMEXIL trials. BJOG : an international journal of obstetrics and gynaecology 121(10): 1263-1273

Appendices

Appendix A – Review protocols

Review protocol for timing of delivery

Field (based on PRISMA-P	Content
PROSPERO registration number	
Review title	Timing of delivery in women with preterm prelabour prolonged rupture of membranes and vaginal or urine group B streptococcus (GBS) detection to reduce risk of early-onset neonatal sepsis
Review question	What is the clinical and cost effectiveness of immediate delivery versus expectant management for women between 34- and 37-weeks gestation with preterm prelabour prolonged rupture of membranes and vaginal or urine group B streptococcus detection during the current pregnancy to reduce the risk of neonatal infection?
Objective	To evaluate the clinical and cost effectiveness of immediate delivery and expectant management in the prevention of early-onset neonatal infection in women between 34+0 and 36+6-weeks gestation with preterm prelabour prolonged rupture of membranes and vaginal or urine group B streptococcus detection during the current pregnancy.
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.
Condition or domain being studied	Neonatal infection is a significant cause of mortality and morbidity in neonates. It may be early-onset (within 72 hours of birth) or late-onset

	(more than 72 hours after birth). Neonatal infection can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths. Pregnant women are not routinely assessed for GBS colonisation status so their status and transmission risk to the baby is not routinely known. In practice there is variation in the decision to provide intrapartum antibiotic prophylaxis. Some centres provide this to all women with preterm prelabour prolonged rupture of membranes, but some only do so for women who have proven GBS colonisation. New evidence has emerged on the impact of timing of delivery on neonatal infection.
Population	Inclusion: • Women with preterm prelabour prolonged rupture of membranes between 34+0 and 37+6 weeks gestation with GBS detected during current pregnancy (using study-defined method of GBS detection) Exclusion: • Women with prelabour rupture of membranes at term
Intervention	• Induction of labour (induced labour or caesarean section after study randomisation)
Comparator	• Expectant management (pregnancy managed until onset of natural labour or clinical signs indicate the need for induction of labour or caesarean section)
Types of study to be included	• RCTs

	• Systematic reviews of RCTs
Other exclusion criteria	Non-English language studies
Context	Hospitals with facilities to care for mothers and neonates
Primary outcomes (critical outcomes)	Neonatal outcomes: • Culture-proven infection from sample taken from the neonate within 72 hours of birth where available or within the study-defined period for early-onset neonatal infection. • suspected bloodstream infection based on clinical symptoms within 72 hours of birth where available or within the study-defined period for early-onset neonatal infection. • mortality (at different time points – peri-natal mortality (stillborn or within 7 days from birth) or greater than 7 days from birth) • duration of antibiotic exposure • health-related quality of life, measured using a validated tool (during the neonatal period and at the latest timepoint reported in study) • hospital length of stay • neonatal respiratory distress syndrome (during the neonatal period) • Maternal outcomes

	• hospital length of stay • psychological distress in baby's family as measured using a validated scale (e.g. parental stressor scale NICU; modified Rutter Malaise Inventory) (during the neonatal period and at the latest timepoint reported in study) • evidence of maternal sepsis (including maternal antibiotic administration) (during pregnancy, birth and within 6 weeks of birth) • number of women given caesarean sections for the current pregnancy
Secondary outcomes (important outcomes)	Not applicable
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.
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.
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
Analysis of sub-groups	Vulnerable women, including: • non-attenders at antenatal clinics • low socioeconomic status (defined using deprivation quintiles) • level of education (based on study definition) • low income (based on study definition) Data will be stratified according to method of delivery (induction of labour or c-section)
Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery

	☐ Other (please specify)		
Language	English		
Country	England		
Anticipated or actual start date	24/06/2019		
Anticipated completion date	12/08/2020		
Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
	Preliminary searches	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
	Piloting of the study selection process	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐

	Formal screening of search results against eligibility criteria	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
	Data extraction	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
	Risk of bias (quality) assessment	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
	Data analysis	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
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)		

Review team members	From the Guideline Updates Team: • Dr Kathryn Hopkins • Dr Clare Dadswell • Mr Fadi Chehadah • Mr Gabriel Rogers • Mr Wesley Hubbard
Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which receives funding from NICE.
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.
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

Other registration details	None
Reference/URL for published protocol	None
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.
Keywords	Immediate delivery, expectant management, preterm prelabour prolonged rupture of membranes, group B streptococcus
Details of existing review of same topic by same authors	None
Current review status	☒ Ongoing
	☐ Completed but not published
	☐ Completed and published

	☐ Completed, published and being updated ☐ Discontinued
Additional information	None
Details of final publication	www.nice.org.uk

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Appendix B – Literature search strategies

Clinical search literature search strategy

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

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

Population and intervention terms

Medline, Medline in Process, Medline E-pubs

1 exp Infant, Newborn/

2 Term Birth/

3 Infant Care/

4 Perinatal Care/

5 Intensive Care Units, Neonatal/

6 Intensive Care, Neonatal/

7 Infant Health/

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

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

10 or/1-9

11 exp Bacterial Infections/

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

13 exp Sepsis/

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

15 (septic* adj4 shock*).tw.

16 or/11-15

17 exp Streptococcus/

18 exp Staphylococcus/

19 (streptococc* or staphylococc*).tw.

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

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

22 exp Escherichia coli/

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

1 24 exp Listeria/
2 25 listeria*.tw.
3 26 exp Klebsiella/
4 27 klebsiella*.tw.
5 28 exp Pseudomonas/
6 29 (pseudomonas or chryseomonas or flavimonas).tw.
7 30 Enterobacteriaceae/
8 31 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw.
9 32 ((enteric or coliform) adj2 bac*).tw.
10 33 exp Neisseria/
11 34 neisseria*.tw.
12 35 exp Haemophilus influenzae/
13 36 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or
14 pfeiffer* or meningitidis)).tw.
15 37 exp Serratia/
16 38 serratia*.tw.
17 39 exp Cronobacter/
18 40 (cronobact* or sakazaki* or malonatic*).tw.
19 41 exp Acinetobacter/
20 42 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw.
21 43 exp Fusobacterium/
22 44 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw.
23 45 exp Enterococcus/
24 46 enterococc*.tw.
25 47 or/17-46
26 48 16 or 47
27 49 10 and 48
28 50 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw.
29 51 ((premature or pre-mature* or preterm or pre-term) adj4 (child* or infant* or baby* or
30 babies* or offspring) adj4 infect*).tw.
31 52 50 or 51
32 53 49 or 52
33 54 exp Fetal Membranes, Premature Rupture/

55 ((preterm* or pre-term* or premature* or pre-mature* or prelabor* or pre-labor* or pre) adj4 (ruptur* or membrane* or disrupt* or erupt* or sever or severed or tear* or breach*)).tw.

56 (prom or proms or pprom*).tw.

57 or/54-56

58 53 and 57

Embase

1 newborn/

2 term birth/

3 infant care/

4 perinatal care/

5 neonatal intensive care unit/

6 newborn intensive care/

7 child health/

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

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

10 or/1-9

11 exp bacterial infection/

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

13 exp sepsis/

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

15 (septic* adj4 shock*).tw.

16 or/11-15

17 exp Streptococcus/

18 exp Staphylococcus/

19 (streptococc* or staphylococc*).tw.

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

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

22 exp Escherichia coli/

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

24 exp Listeria/

25 listeria*.tw.

26 exp Klebsiella/

27 klebsiella*.tw.

28 exp Pseudomonas/

29 (pseudomonas or chryseomonas or flavimonas).tw.

30 exp Enterobacteriaceae/

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

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

33 exp Neisseria/

34 neisseria*.tw.

35 exp Haemophilus influenzae/

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

37 exp Serratia/

38 serratia*.tw.

39 exp cronobacter/

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

41 exp Acinetobacter/

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

43 exp Fusobacterium/

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

45 exp Enterococcus/

46 enterococc*.tw.

47 or/17-46

48 16 or 47

49 10 and 48

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

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

52 50 or 51

53 49 or 52

54 premature fetus membrane rupture/

55 ((preterm* or pre-term* or premature* or pre-mature* or prelabor* or pre-labor* or pre) adj4 (ruptur* or membrane* or disrupt* or erupt* or sever or severed or tear* or breach*)).tw.

56 (prom or proms or pprom*).tw.

57 or/54-56

58 53 and 57

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

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

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

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

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

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

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

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

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

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

#10 {or #1-#9}

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

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

#13 MeSH descriptor: [Sepsis] explode all trees

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

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

#16 {or #11-#15}

#17 MeSH descriptor: [Streptococcus] explode all trees

#18 MeSH descriptor: [Staphylococcus] explode all trees

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

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

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

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

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

#24 MeSH descriptor: [Listeria] explode all trees

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

#26 MeSH descriptor: [Klebsiella] explode all trees

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

#28 MeSH descriptor: [Pseudomonas] explode all trees

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

#30 MeSH descriptor: [Enterobacteriaceae] explode all trees

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

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

#33 MeSH descriptor: [Neisseria] explode all trees

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

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

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

#37 MeSH descriptor: [Serratia] explode all trees

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

#39 MeSH descriptor: [Cronobacter] explode all trees

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

#41 MeSH descriptor: [Acinetobacter] explode all trees

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

#43 MeSH descriptor: [Fusobacterium] explode all trees

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

#45 MeSH descriptor: [Enterococcus] explode all trees

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

#47 {or #17-#46}

#48 #16 or #47

#49 #10 and #48

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

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

#52 #50 or #51

#53 #49 or #52

#54 MeSH descriptor: [Fetal Membranes, Premature Rupture] explode all trees

#55 ((preterm* or pre-term* or premature* or pre-mature* or prelabor* or pre-labor* or pre) near/4 (ruptur* or membrane* or disrupt* or erupt* or sever or severed or tear* or breach*)):ti,ab,kw

#56 (prom or proms or pprom*):ti,ab,kw

#57 #54 or #55 or #56

#58 #53 and #57

#59 "conference":pt or (clinicaltrials or trialsearch):so

#60 #58 not #59

DARE

1 (MeSH DESCRIPTOR Infant, Newborn EXPLODE ALL TREES)

2 (MeSH DESCRIPTOR Term Birth)

3 (MeSH DESCRIPTOR Infant Care)

4 (MeSH DESCRIPTOR Perinatal Care)

5 (MeSH DESCRIPTOR Intensive Care Units, Neonatal)

6 (MeSH DESCRIPTOR Intensive Care, Neonatal)

7 (MeSH DESCRIPTOR Infant Health)

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

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

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

11 (MeSH DESCRIPTOR Bacterial Infections EXPLODE ALL TREES)

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

13 (MeSH DESCRIPTOR Sepsis EXPLODE ALL TREES)

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

15 (((septic* NEAR4 shock*)))

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

17 (MeSH DESCRIPTOR Streptococcus EXPLODE ALL TREES)

18 (MeSH DESCRIPTOR Staphylococcus EXPLODE ALL TREES)

19 (((streptococc* or staphylococc*)))

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

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

22 (MeSH DESCRIPTOR Escherichia coli EXPLODE ALL TREES)

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

24 (MeSH DESCRIPTOR Listeria EXPLODE ALL TREES)

25 ((listeria*))

26 (MeSH DESCRIPTOR Klebsiella EXPLODE ALL TREES)

27 ((klebsiella*))

28 (MeSH DESCRIPTOR Pseudomonas EXPLODE ALL TREES)

29 (((pseudomonas or chryseomonas or flavimonas)))

30 (MeSH DESCRIPTOR Enterobacteriaceae EXPLODE ALL TREES)

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

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

33 (MeSH DESCRIPTOR Neisseria EXPLODE ALL TREES)

34 ((neisseria*))

35 (MeSH DESCRIPTOR Haemophilus influenzae EXPLODE ALL TREES)

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

37 (MeSH DESCRIPTOR Serratia EXPLODE ALL TREES)

38 ((serratia*))

39 (MeSH DESCRIPTOR Cronobacter EXPLODE ALL TREES)

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

41 (MeSH DESCRIPTOR Acinetobacter EXPLODE ALL TREES)

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

43 (MeSH DESCRIPTOR Fusobacterium EXPLODE ALL TREES)

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

45 (MeSH DESCRIPTOR Enterococcus EXPLODE ALL TREES)

46 ((enterococc*))

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

48 (#16 OR #47)

49 (#10 AND #48)

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

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

52 (#50 OR #51)

53 (#49 OR #52)

54 MeSH DESCRIPTOR Fetal Membranes, Premature Rupture EXPLODE ALL TREES

55 (((preterm* or pre-term* or premature* or pre-mature* or prelabor* or pre-labor* or pre) near4 (ruptur* or membrane* or disrupt* or erupt* or sever or severed or tear* or breach*)))

56 (prom or proms or pprom*)

57 #54 OR #55 OR #56

58 #53 AND #57

59 (#58) IN DARE

Search Filters

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

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

Randomised Controlled Trial

1. randomized controlled trial.pt.

2. randomi?ed.mp.

3. placebo.mp.

4. or/1-3

Systematic Review

1 MEDLINE or pubmed).tw.

2 systematic review.tw.

3 systematic review.pt.

4 meta-analysis.pt.

5 intervention$.ti.

6 or/1-5

Health Economics literature search strategy

Sources searched to identify economic evaluations

- MEDLINE (Ovid)
- MEDLINE in Process (Ovid)

- Medline E-pubs (Ovid)
- Embase (Ovid)
- EconLit (Ovid)

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

Health economics search strategy

Database: Medline (Ovid)
1 exp Infant, Newborn/ (607120)
2 Term Birth/ (2958)
3 Infant Care/ (9209)
4 Perinatal Care/ (4613)
5 Intensive Care Units, Neonatal/ (14748)
6 Intensive Care, Neonatal/ (5673)
7 Infant Health/ (783)
8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (394580)
9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (50922)
10 or/1-9 (791905)
11 exp Bacterial Infections/ (886598)
12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (148920)
13 exp Sepsis/ (123123)
14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (100090)
15 (septic* adj4 shock*).tw. (19697)
16 (bacter?emia* or bacill?emia*).tw. (26877)
17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (38725)
18 or/11-17 (1097119)
19 exp Streptococcus/ (78627)
20 exp Staphylococcus/ (104852)
21 (streptococc* or staphylococc*).tw. (206696)
22 (GBS or MRSA or NRCS-A or MSSA).tw. (27020)

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

24 exp Escherichia coli/ (278943)

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

26 exp Listeria/ (15143)

27 listeria*.tw. (18688)

28 exp Klebsiella/ (19836)

29 klebsiella*.tw. (26962)

30 exp Pseudomonas/ (71592)

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

32 Enterobacteriaceae/ (18945)

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

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

35 exp Neisseria/ (20482)

36 neisseria*.tw. (18785)

37 exp Haemophilus influenzae/ (13731)

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

39 exp Serratia/ (6599)

40 serratia*.tw. (8439)

41 exp Cronobacter/ (655)

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

43 exp Acinetobacter/ (9822)

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

45 exp Fusobacterium/ (3796)

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

47 exp Enterococcus/ (19718)

48 enterococc*.tw. (26150)

49 or/19-48 (765874)

50 18 or 49 (1614537)

51 10 and 50 (65444)

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

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

54 52 or 53 (16770)

55 51 or 54 (74853)

56 Economics/ (27206)

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

58 Economics, Dental/ (1911)

59 exp Economics, Hospital/ (24558)

60 exp Economics, Medical/ (14206)

61 Economics, Nursing/ (3999)

62 Economics, Pharmaceutical/ (2941)

63 Budgets/ (11315)

64 exp Models, Economic/ (15053)

65 Markov Chains/ (14321)

66 Monte Carlo Method/ (28322)

67 Decision Trees/ (11133)

68 econom$.tw. (238765)

69 cba.tw. (9764)

70 cea.tw. (20532)

71 cua.tw. (999)

72 markov$.tw. (17997)

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

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

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

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

77 budget$.tw. (23716)

78 expenditure$.tw. (49355)

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

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

81 or/56-80 (926379)

82 "Quality of Life"/ (194718)

83 quality of life.tw. (229884)

84 "Value of Life"/ (5706)

85 Quality-Adjusted Life Years/ (12284)

86 quality adjusted life.tw. (10842)

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

88 disability adjusted life.tw. (2741)

89 daly$.tw. (2486)

90 Health Status Indicators/ (23409)

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

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

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

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

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

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

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

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

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

100 utilit$.tw. (171457)

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

102 disutili$.tw. (396)

103 rosser.tw. (94)

104 quality of wellbeing.tw. (14)

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

106 qwb.tw. (190)

107 willingness to pay.tw. (4500)

108 standard gamble$.tw. (783)

109 time trade off.tw. (1037)

110 time tradeoff.tw. (238)

111 tto.tw. (899)

112 or/82-111 (493012)

113 81 or 112 (1350947)

114 55 and 113 (3480)

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

116 animals/ not humans/ (4686781)

117 115 not 116 (213)

118 limit 117 to english language (208)

1

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)

1

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)

1

2

3

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)

1

Database: Econlit (Ovid)

1 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (732)

2 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (45)

3 1 or 2 (767)

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

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

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

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

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

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

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

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

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

13 listeria*.tw. (6)

14 klebsiella*.tw. (0)

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

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

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

18 neisseria*.tw. (1)

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

20 serratia*.tw. (0)

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

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

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

24 enterococc*.tw. (5)

25 or/4-24 (194)

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

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

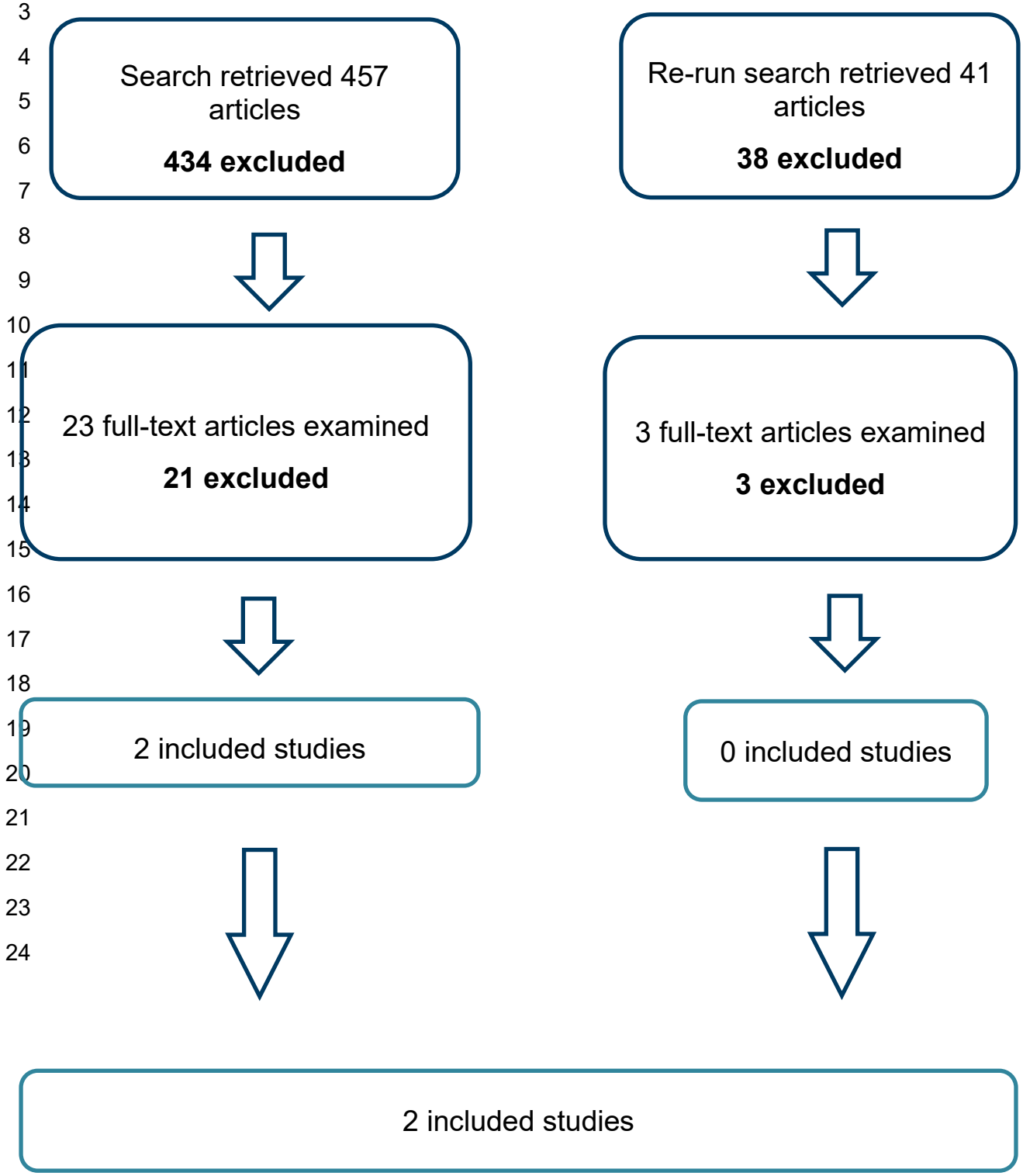
28 26 or 27 (12)

29 25 or 28 (205)

30 3 and 29 (15)

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

Appendix C – Effectiveness evidence study selection



1 Appendix D – Effectiveness evidence

Morris, 2016

Bibliographic Reference	Morris, Jonathan M; Roberts, Christine L; Bowen, Jennifer R; Patterson, Jillian A; Bond, Diana M; Algert, Charles S; Thornton, Jim G; Crowther, Caroline A; PPROMT Collaboration; Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPROMT trial): a randomised controlled trial.; Lancet (London, England); 2016; vol. 387 (no. 10017); 444-52

2 Study details

Study type	Randomised controlled trial (RCT)
Study location	11 countries (Australia, New Zealand, Argentina, South Africa, Brazil, UK, Norway, Egypt, Uruguay, Poland, and Romania)
Study setting	65 centres with the facilities to provide care for mothers and neonates born at 34 weeks, including the availability of respiratory support
Study dates	May 2004 - June 2013
Duration of follow-up	Neonatal outcomes: 28 days or until discharge (whichever was first) Maternal outcomes: Not reported
Sources of funding	Australian NHMRC Project Grants Women's and Children's Hospital Foundation, Adelaide
Inclusion criteria	Women between 34- and 36-weeks gestation with PPROM and a singleton pregnancy Women with ruptured membranes prior to 34 weeks gestation could be included if their latency period extended to 34 weeks *Results for women with group B streptococcus detected (from vaginal swab after PPROM and at or before randomisation) were reported separately*
Exclusion criteria	Women with meconium-stained amniotic fluid Women in established labour Clinical evidence of chorioamnionitis Antepartum haemorrhage Any other contraindication to expectant management
Sample size	1839
Outcome measures	Neonatal sepsis Definite or probable *Definite - Definite systemic neonatal sepsis was defined as a positive culture of a known pathogen from blood or cerebrospinal fluid for which the baby was treated with antibiotics for 5 or more days (or died before 5 days), and the presence of one or more clinical signs of infection*

	Probable – presence of clinical signs for which the baby was treated with antibiotics for 5 or more days together with one or more of an abnormal full blood count; abnormal C-reactive protein; positive Group B streptococcus antigen on bladder tap urine, blood, or CSF; elevated CSF white cellcount5 (CSF white cell count >100 × 10^6 cells per L); growth of a known virulent pathogen (eg, Group B streptococcus, Escherichia coli, or Listeria) from a surface swab; or a histological diagnosis of pneumonia in an early neonatal death

1

2 **Study arms**

Immediate delivery (N = 923 total; 88 with GBS)

Delivery as close to randomisation as possible, preferably within 24 hours. Delivery could be via spontaneous labour, after labour induction or caesarean. Antibiotics were prescribed according to local protocols - 92% of women were prescribed antibiotics before delivery (. No information provided on the specific antibiotics prescribed

Loss to follow-up	1 (information only provided for all women randomised. No specific information for GBS subgroup)
% Female	100%
Mean maternal age (SD)	27.9 (6.2) (information only provided for all women randomised. No specific information for GBS subgroup)
Gestational age at birth (n, %)	34 weeks 315 (34%); 35 weeks 273 (30%); 36 weeks 306 (33%); 37 weeks 23 (2%); 38 weeks 1 (<1%); 39 weeks 1 (<1%); 40 weeks 1 (<1%); 41 weeks 3 (<1%) (information only provided for all women randomised. No specific information for GBS subgroup)

Expectant management (N = 915 total; 83 with GBS)

Birth occurred after spontaneous labour, at term or when the clinician felt necessary based on clinical indications. Managed according to local guidelines. Delivery could be via spontaneous labour, after labour induction or caesarean. Antibiotics were prescribed according to local protocols - 93% of women were prescribed antibiotics before delivery. No information provided on the specific antibiotics prescribed

Loss to follow-up	1 (information only provided for all women randomised. No specific information for GBS subgroup)
% Female	100%
Mean maternal age (SD)	28.0 (6.2) (information only provided for all women randomised. No specific information for GBS subgroup)

	Gestational age at birth (n, %)	34 weeks 161 (18%); 35 weeks 268 (29%); 36 weeks 295 (32%); 37 weeks 174 (19%); 38 weeks 7 (1%); 39 weeks 2 (<1%); 40 weeks 5 (1%); 41 weeks 0 (information only provided for all women randomised. No specific information for GBS subgroup)

Risk of bias

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Moderate

Limited information about GBS subgroup so baseline characteristics can't be compared

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

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Moderate

Limited information provided about GBS subgroup. Results of early-onset and late-onset neonatal infection not separated

Overall Directness

Partially directly applicable

Reports neonatal sepsis but does not report time scale (early-or late-onset)

Tajik, 2014

Bibliographic Reference	Tajik, P; van der Ham, D P; Zafarmand, M H; Hof, M H P; Morris, J; Franssen, M T M; de Groot, C J M; Duvekot, J J; Oudijk, M A; Willekes, C; Bloemenkamp, K W M; Porath, M; Woiski, M; Akerboom, B M; Sikkema, J M; Nij Bijvank, B; Mulder, A L M; Bossuyt, P M; Mol, B W J; Using vaginal Group B Streptococcus colonisation in women with preterm premature rupture of membranes to guide the decision for immediate delivery: a secondary analysis of the PPROMEXIL trials.; BJOG : an international journal of obstetrics and gynaecology; 2014; vol. 121 (no. 10); 1263-1273

1 Study details

Study type	Randomised controlled trial (RCT)
Study location	Netherlands
Study setting	8 academic and 52 non-academic hospitals
Study dates	January 2007 - September 2009
Duration of follow-up	Within 72 hours after birth
Sources of funding	The Netherlands Organisation for Health Research and Development (Zon-Mw), The Hague, The Netherlands
Inclusion criteria	Women with a singleton or twin pregnancy Presenting with PPROM between 34+0 and 36+6 weeks of gestation and not in labour within 24 hours after rupture of membranes Women diagnosed with PPROM after 26+0 weeks but who had not delivered by 34+0 weeks of gestational age *Results for women with group B streptococcus detected (from vaginal swab at study entry or at hospital admission) were reported separately*
Exclusion criteria	Women with a monochorionic multiple pregnancy Women with an abnormal (non-reassuring) cardiotocogram Women with meconium-stained amniotic fluid Signs of intrauterine infection Major fetal abnormalities Hemolysis Elevated liver enzymes Low platelets (HELLP syndrome) Severe preeclampsia
Sample size	776

Outcome measures	Early-onset neonatal infection Proven or suspected *positive blood culture taken at birth (not Staphylococcus epidermidis) or, within 72 hours, two or more symptoms of infection (apnoea, temperature instability, lethargy, feeding intolerance, respiratory distress, haemodynamic instability) plus one of the following three items: (i) positive blood culture, (ii) C-reactive protein >20 mmol/l, or (iii) positive surface cultures of a known virulent pathogen* Neonatal length of stay Neonatal respiratory distress syndrome Caesarean section

1

2 **Study arms**

Expectant management (N = 359 total; 46 with GBS)

Monitored according to local protocol until spontaneous delivery in an outpatient or inpatient setting. Monitoring included at least daily maternal temperature monitoring and twice weekly blood sampling for maternal leukocyte count and C-reactive protein measurement. At 37+0 weeks of gestational age, labour was induced according to national guidelines. If cesarean section was indicated this was performed as soon as labour commenced. Labour was induced prior to 37+0 weeks of gestation if there were clinical signs of infection or other indications that required induction of labour. Antibiotics were given according to local protocols, either based on observation while waiting for culture results or given dependant on culture results – 77% of women with GBS colonisation were given antibiotics (overall outcome - no information provided for individual trial arms)

Loss to follow-up	0
% Female	100%
Mean maternal age (SD)	26.6 (5.6) (information only provided for all women randomised. No specific information for GBS subgroup)
Median gestational age at birth (weeks) (IQR)	36+4 (35+6 – 37+0) (information only provided for all women randomised. No specific information for GBS subgroup)

Immediate delivery (N = 364 total; 57 with GBS)

Induced within 24 hours of randomisation. Induction was performed according to national guidelines. After vaginal examination labour was induced with either prostaglandin or oxytocin. Any planned cesarean sections took place as soon as possible after randomisation. Antibiotics were given according to local protocols, either based on observation while waiting for culture results or given dependant on

	culture results – 77% of women with GBS colonisation were given antibiotics (overall outcome - no information provided for individual trial arms)	
	Loss to follow-up	0
	% Female	100%
	Mean maternal age (SD)	29.5 (4) (information only provided for all women randomised. No specific information for GBS subgroup)
	Median gestational age at birth (weeks) (IQR)	36+0 (35+1 – 36+4) (information only provided for all women randomised. No specific information for GBS subgroup)

Risk of bias

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Some concerns

(Original study was randomised but post-hoc only uses a subset of patients. Baseline characteristics for post-hoc patients are not reported)

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

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Post-hoc analysis by GBS status was not stated in the original analysis plan)

Overall bias and Directness

Risk of bias judgement

Some concerns

(Post-hoc analysis of a subgroup that was not previously defined in the analysis plan. Baseline characteristics of the GBS subgroup not reported)

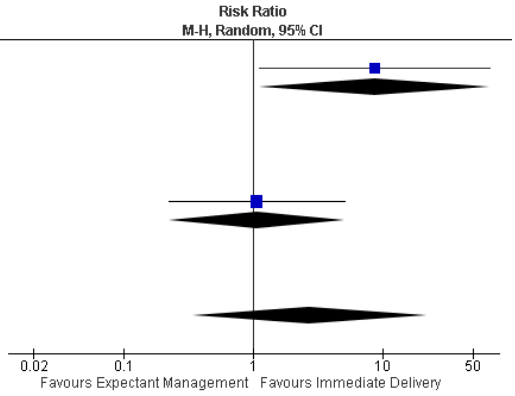
Overall Directness

Directly applicable

Appendix E – Forest plots

Neonatal Infection (confirmed or suspected)

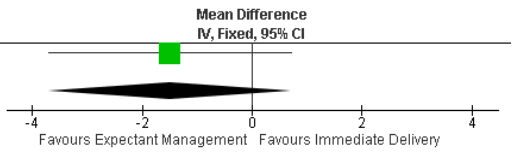
Study or Subgroup	Expectant Management Events	Total	Immediate Delivery Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Early-onset neonatal infection						
Tajik 2014 (1)	7	46	1	57	45.0%	8.67 [1.11, 67.98]
Subtotal (95% CI)		**46**		**57**	**45.0%**	**8.67 [1.11, 67.98]**
Total events	7		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.06 (P = 0.04)						
1.3.2 Neonatal sepsis (early- or late- onset not specified)						
Morris 2016 (2)	3	83	3	88	55.0%	1.06 [0.22, 5.11]
Subtotal (95% CI)		**83**		**88**	**55.0%**	**1.06 [0.22, 5.11]**
Total events	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.07 (P = 0.94)						
Total (95% CI)		**129**		**145**	**100.0%**	**2.73 [0.34, 22.18]**
Total events	10		4			
Heterogeneity: Tau² = 1.43; Chi² = 2.64, df = 1 (P = 0.10); I² = 62%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Test for subgroup differences: Chi² = 2.53, df = 1 (P = 0.11), I² = 60.5%						



Footnotes
(1) Proven or suspected infection
(2) Definite or probable infection

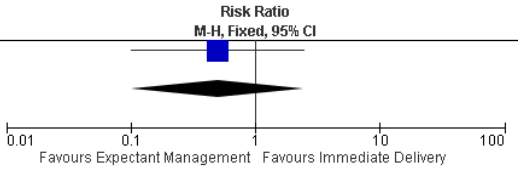
Neonatal length of stay (days)

Study or Subgroup	Expectant Management Mean	SD	Total	Immediate Delivery Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tajik 2014	6.6	5.3	46	8.1	6.1	57	100.0%	-1.50 [-3.70, 0.70]
Total (95% CI)			**46**			**57**	**100.0%**	**-1.50 [-3.70, 0.70]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.33 (P = 0.18)								



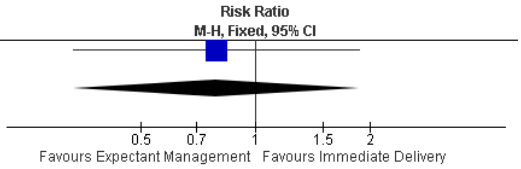
Neonatal respiratory distress syndrome

Study or Subgroup	Expectant Management Events	Total	Immediate Delivery Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tajik 2014	2	46	5	57	100.0%	0.50 [0.10, 2.44]
Total (95% CI)		**46**		**57**	**100.0%**	**0.50 [0.10, 2.44]**
Total events	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						



Number of women given caesarean sections

Study or Subgroup	Expectant Management Events	Total	Immediate Delivery Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tajik 2014	7	46	11	57	100.0%	0.79 [0.33, 1.87]
Total (95% CI)		**46**		**57**	**100.0%**	**0.79 [0.33, 1.87]**
Total events	7		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						



Appendix F – GRADE table

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

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (expectant management)	Absolute risk (immediate delivery)	Risk of bias	Inconsistency	Indirectness	Quality
Neonatal infection (confirmed or suspected) (RR <1 favours expectant management)									
Early-onset neonatal infection									
1 (Tajik 2014)	Parallel RCT	103	RR 8.67 (1.11, 67.98)	15 per 100	2 per 100 (0, 14)	Serious[1]	N/A[4]	Not serious	Moderate
Neonatal sepsis (early- or late- onset not specified)									
1 (Morris 2016)	Parallel RCT	171	RR 1.06 (0.22, 5.11)	4 per 100	3 per 100 (1, 16)	Serious[1]	N/A[4]	Serious[2]	Low
Neonatal infection (early-onset neonatal infection and neonatal sepsis)									
2 (Tajik 2014, Morris 2016)	Parallel RCTs	274	RR 2.73 (0.34, 22.18)	8 per 100	3 per 100 (0, 23)	Serious[1]	Serious[3]	Serious[2]	Very low
Neonatal length of stay (days) (MD <0 favours expectant management)									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (expectant management)	Absolute risk (immediate delivery)	Risk of bias	Inconsistency	Indirectness	Quality
1 (Tajik 2014)	Parallel RCT	103	MD -1.50 (-3.70, 0.70)	-	-	Serious[1]	N/A[4]	Not serious	Moderate
Neonatal respiratory distress syndrome (RR <1 favours expectant management)									
1 (Tajik 2014)	Parallel RCT	103	RR 0.50 (0.10, 2.44)	4 per 100	9 per 100 (2, 43)	Serious[1]	N/A[4]	Not serious	Moderate
Number of women given caesarean sections (RR <1 favours expectant management)									
1 (Tajik 2014)	Parallel RCT	103	RR 0.79 (0.33, 1.87)	15 per 100	19 per 100 (8, 46)	Serious[1]	N/A[4]	Not serious	Moderate

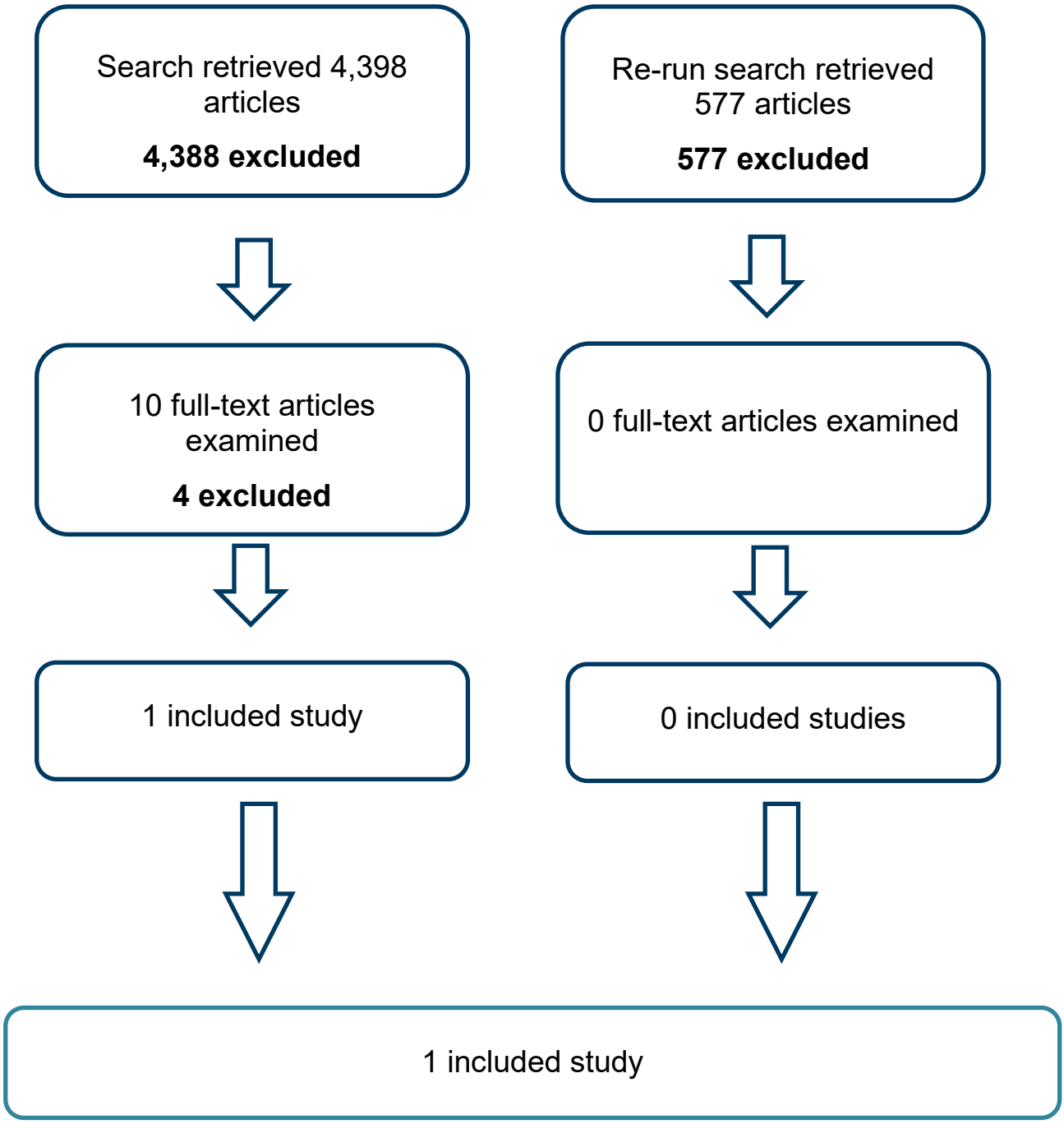
1. Single study at moderate risk of bias. Quality downgraded 1 level

2. Single study which is partially applicable to the research question. Quality downgraded 1 level

3. I^2 between 33.3% - 66.7%. Quality downgraded 1 level

4. Single study. Inconsistency not applicable

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

Table 1: Lain et al (2017)

Lain et al. (2017) An economic evaluation of planned immediate versus delayed birth for preterm prelabour rupture of membranes: findings from the PPROMT randomised controlled trial.

Study details	**Analysis:** Cost-effectiveness analysis **Approach to analysis:** An economic evaluation of planned immediate versus delayed birth for preterm prelabour rupture of membranes: findings from the PPROMT randomised controlled trial (Morris et al. 2016). **Effects:** 1) Neonatal sepsis (any time before infants discharged); 2) Neonatal respiratory distress syndrome (NRDS). **Perspective:** Costs to the health system. **Time horizon:** The model only accounted for the immediate effects with strategy within the same year. **Discounting:** Discounting was not applied as the time horizon of costs and outcomes were in the same year.
Interventions	**Intervention 1:** Expectant management **Intervention 2:** Immediate delivery **Analysis 1:** Sepsis **Analysis 2:** RDS
Population	**Population:** Women with a singleton pregnancy with ruptured membranes between 34+0 and 36+6 weeks gestation. Women were recruited from Australia, the UK, Argentina, New Zealand, South Africa and 6 other countries. **Characteristics:** as per Morris et al. (2016) – see appendix D
Data sources	**Resource use:** Resource-use data included number of days in hospital, days in new-born intensive care, antenatal outpatient service use, number and type of diagnostic investigations, and treatment for each mother infant from PPROMT trial. **Baseline/natural history:** NR **Effectiveness:** From PPROMT randomised controlled trial. **Costs:** Within-RCT resource-use (antenatal care, delivery, postnatal length of stay). Unit costs from NHS RefCosts (UK) used for women from the UK and other countries and Australian costs used for women from Australia and New Zealand. **QoL:** Not a cost–utility analysis.
Base-case results	***2012* UK pounds sterling**

Analysis	Intervention	Absolute		Incremental		
		Costs (£)	QALYs	Costs (£)	Effects	ICER
Analysis 1	Expectant	-	-			
	Immediate	-	-	£112 (-£431, £662)	-0.007 (-0.02, 0.01)	£16,000 per sepsis prevented
Analysis 2	Expectant	-	-			
	Immediate	-	-	As above	0.03 (0.01, 0.06)	Dominated

Sensitivity analyses	**Deterministic:** Analysis using UK-only resource-use data produced relatively similar – though more uncertain – estimate of difference in total costs (308 [−801 to 1530]). **Probabilistic:** Bootstrap using 5,000 resamples to estimate 95% CI.
Comments	**Source of funding:** Australian NHMRC Project Grants. **Limitations:** Serious limitations (appendix H, Table 2)

Abbreviations: RDS, respiratory distress syndrome

Table 2: Economic evaluation checklist Lain et al (2017)

Category	Rating	Comments
Applicability		
1.1 Is the study population appropriate for the review question?	Partly	UK population is a proportion of the study (22%)
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?	Partly	UK setting is a proportion of the study (22%)
1.4 Is the perspective for costs appropriate for the review question?	Partly	UK cost data were used for UK and other countries. Australian dollars were used for Australia and New Zealand
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	No	Discounting was not applied as the time horizon of costs and outcomes were in the same year
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).	No	Not a cost–utility analysis
1.8 OVERALL JUDGEMENT	**PARTIALLY 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?	No	The model only evaluates immediate outcomes with each intervention that occur within the same year.
2.3 Are all important and relevant outcomes included?	Partly	The model only accounts for sepsis and RDS as outcomes. It does not consider any long-term outcomes that occur as a consequence of sepsis or RDS.
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	From a single clinical trial
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	Relative intervention effects come from a single clinical trial.
2.6 Are all important and relevant costs included?	Partly	The model only accounts for costs of each intervention and the outcomes it considers. As such it does not account for costs of outcomes that were not considered, such as long term consequences that occur as a result of sepsis or RDS.
2.7 Are the estimates of resource use from the best available source?	Partly	Estimates of resource use come from a single clinical trial.
2.8 Are the unit costs of resources from the best available source?	Partly	Costs from UK NHS RefCosts were used for the UK and all other countries except Australia and New Zealand, which used Australian costs.
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	**SERIOUS LIMITATIONS**	

1

Appendix I - Health economic model

I.1 Model overview

The objective of this analysis is to compare the benefits, harms and costs of immediate delivery versus expectant management in women between 34- and 37-week gestation with preterm prelabour prolonged rupture of membranes and vaginal or urine GBS detection.

I.1.1 Population(s)

The target population in the model is women between 34- and 37-week gestation with preterm prelabour prolonged rupture of membranes and vaginal/urine GBS detection.

I.1.2 Interventions

The model compares 2 interventions based on the timing of the delivery: immediate delivery versus expectant management. These strategies should be understood in terms of the intended approach rather than actual outcome: in the RCTs from which we draw our effectiveness data, some women who were randomised to expectant management gave birth very soon afterwards, and some who were randomised to immediate delivery experienced nontrivial delays before it was possible for them to give birth.

I.1.3 Type of evaluation, time horizon, perspective

The model is a cost–utility analysis (CUA). We measure outcomes in quality-adjusted life years (QALYs). We express the incremental cost-effectiveness ratio (ICER) as a cost per QALY gained.

The model has a lifetime horizon, to reflect all important differences in costs and outcomes between the interventions being compared. Nevertheless, all relevant transitions in the model happen within the first 72 hours of birth.

The analysis adopts a UK NHS and Personal Social Services (PSS) perspective.

I.1.4 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. We designed the model structure to reflect the clinical evidence from RCTs (Morris et al., 2016; Tajik et al., 2014).

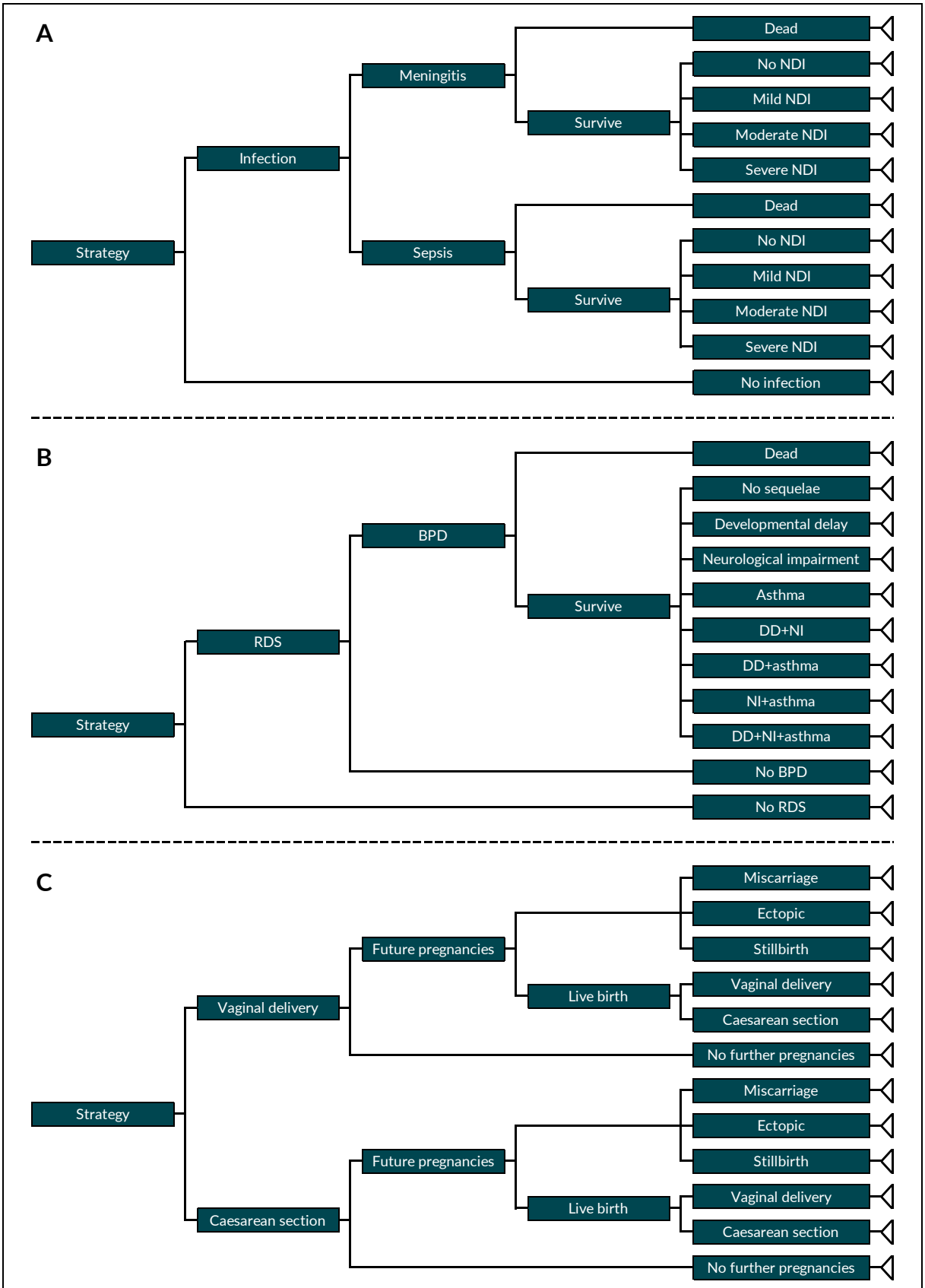
The model focuses on the trade-off between the 2 strategies, immediate delivery or expectant management. Expectant management may be associated with higher risk of neonatal infection. However, babies born earlier (as will be the case in the immediate delivery strategy) have an increased risk of problems associated with prematurity. We use neonatal respiratory distress syndrome (RDS) as a proxy indicator of this risk, and estimate the long-term consequences with which it is associated. We also use evidence that rates of caesarean section may be different between the 2 approaches.

The model comprises 3 independent decision-trees:

- The first determines the risk of infection among babies, using evidence from the RCTs synthesised in the clinical review. The babies in our simulated population have a high risk of GBS infection due to the mother's GBS detection. The model subdivides infections into meningitis and sepsis, both of which are associated with long-term disability or death.
- The second decision-tree calculates the proportion of babies experiencing health effects of prematurity. To estimate this, we use rates of RDS, as reported in the underlying RCTs, as a proxy measure. We then project long-term sequelae, using evidence of lifelong health problems with which RDS is associated. We do not assume this relationship is necessarily causal; rather, we use RDS rates as an indicator of the kind of problems faced by late-preterm infants, some of which have lasting consequences. To estimate long-term impairment, we use evidence on chronic lung disease ('bronchopulmonary dysplasia') and its consequences. Although the committee advised that, in neonates of the relatively mature gestational age represented in our decision problem, 'bronchopulmonary dysplasia' is not commonly used as a diagnostic label, it has been used as an outcome in at least 1 large RCT in this age-group (Gyamfi-Bannerman et al. 2016). Moreover, there is clear evidence that late-preterm infants experience higher rates of neurodevelopmental morbidity than those born at term (Quigley et al. 2012, Chan et al. 2016, Allotey et al. 2018), and there is also some evidence that this relationship is at least partially mediated by neonatal respiratory dysfunction (Wachtel et al. 2015). This approach enables us to take advantage of a short-term outcome that is reported in relevant RCTs (none of which have long-term follow-up data) in order to estimate lifelong impacts.
- The final decision-tree simulates outcomes relating to the mode of delivery. The model determines the likelihood of caesarean section or vaginal birth, using evidence from included RCTs. The model then considers the potential impact of caesarean section on future pregnancies, including costs associated with future deliveries (which are more likely to be caesarean sections if the index birth was a caesarean), and costs and QALY loss due to adverse pregnancy outcomes (using evidence that risks of ectopic pregnancy, miscarriage and stillbirth are increased in women with a history of caesarean section).

The model evaluates the 3 decision-trees independently – that is, we assume no relationship between the outcomes in each – and combines results to estimate net costs and QALYs across each domain.

Figure HE001 provides a schematic depiction of the model structure.



DD = developmental delay; NDI = neurodevelopmental impairment; NI = neurological impairment
The model comprises 3 independent decision-trees, simulating (A) infections and their sequelae, (B) RDS and its sequelae and (C) mode of delivery and its impact on subsequent pregnancies.

Figure HE001: Structure of original cost–utility model

I.3 Parameters

I.3.1 General approach

I.3.1.1 Identifying sources of parameters

With the exception of effectiveness data (which came from the clinical review; see above) and the economic evaluation by Lain et al. (2017) (which we identified in the systematic review of cost–utility analyses conducted for this research question; see above), 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 CUAs identified in our systematic review (see above); during the review, 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.

In cases where there was paucity of published literature for values essential to parameterise key aspects of the model, we obtained data from unpublished sources; further details are provided below.

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 Cohort parameters

I.3.2.1 Starting demographics and characteristics

We based the modelled cohort's baseline characteristics on a large trial, PPROMT (N=1835; Morris et al. 2016). The mean age of mothers is 27.95 (SD 6.2) years. Only 10% of the expectant mothers from the PPROMT trial had previous caesarean delivery. 47% of mothers had no previous pregnancies.

I.3.3 Baseline clinical data and natural history

I.3.3.1 Short-term events

Infection

As shown in Table HE003, the model assumes baseline infection risk (for expectant management) of 15% (7/46), taken from risk of early-onset infection in mothers colonised with GBS in Tajik et al. (2014). We preferred this source as the population had prolonged (>24-hour) rupture of membranes, in line with our decision problem. This was not an eligibility criterion in the larger RCT (Morris et al. 2016), which included all cases with clinically suspected rupture of membranes. While the committee agreed that this distinction was unlikely to have any meaningful influence on the **relative** effects of the 2 approaches (and was happy to pool data from both for that purpose; see I.3.4.1), committee members advised that the same could not be said of the **absolute** probability of infection. Therefore, the committee agreed that the higher risk of infection observed in Tajik et al. (2014) was the more appropriate value for our population. We explore the impact of abandoning this distinction, by using a pooled estimate from the GBS+ subgroups of both RCTs in a scenario analysis.

Table HE003: Infection risk

	Risk	Source
Base case		
GBS+, prolonged PPROM	15.2% (7/46)	Tajik et al. (2014)
Alternative value (scenario analysis)		
GBS+ trial-arms pooled[a]	7.9% (5.3% to 17.2%)	Tajik et al. (2014) & Morris et al. (2016)

(a) fixed-effect meta-analysis on log-odds scale

Risk of meningitis given infection

In common with previous analyses of neonatal infection (Colbourn et al. 2007, CG149), the model subdivides infections into meningitis and sepsis. In order to do this, the model requires an estimate of the probability that any given infection will be meningitis, with sepsis assumed to represent the remainder of cases (this is consistent with the definitions used in the RCTs, which required clinical symptoms to be present to classify a case as an infection).

Table HE004 summarises the different potential sources for conditional probability of meningitis, given infection. For our base case, we assume a 11% probability, which we took from a surveillance cohort in the UK and Ireland (O'Sullivan et al. 2019). Because other values we identified for the same parameter were very similar, we did not explore them as alternative model inputs.

Table HE004: Risk of meningitis

	Risk of meningitis	Source
Base case		
Given early onset GBS	0.110 (57/517)	O'Sullivan et al. (2018)
Alternative values (not used)		
Given early onset GBS	0.118 (12/102)	Schroeder et al. (2009)
Given early onset GBS preterm	0.101 (95% CI 0.056 to 0.156)	Colbourn et al. (2007)
Given early onset GBS term	0.119 (95% CI 0.081 to 0.164)	Colbourn et al. (2007)

Risk of respiratory distress syndrome (RDS)

The model assumes baseline RDS risk (for immediate delivery) of 8.0%, taken from a pooled analysis of the immediate delivery arms from the RCTs (Table HE005). The committee advised that there is no reason to suspect that the mother's GBS status would have any meaningful effect on the probability that their baby will experience RDS. Therefore, we pool data from the full sample of each RCT. Data from Tajik et al. (2014) can be stratified according to maternal GBS status, and confirm the committee's expectation that there is unlikely to be a meaningful difference in RDS rates according to this factor.

Table HE005: Probability of RDS

	Risk
Morris et al. (2016)	8.3% (76/919)
Tajik et al. (2014) (GBS+ only)	8.8% (5/57)
Tajik et al. (2014) (GBS-)	6.9% (21/306)
Trial-arms pooled[a]	**8.0% (95%CI: 6.6 to 9.6%)**

(a) fixed-effect meta-analysis performed on log-odds scale before transforming back to natural probabilities

Risk of bronchopulmonary dysplasia (BPD) given RDS

The model assumes that a proportion of babies with RDS will develop BPD, which may, in turn, lead to mortality and long-term morbidity. Consequently, we require an estimate of the conditional probability of BPD given RDS. We were unable to find any published research directly addressing this question in the population in which we are interested (that is, relatively late-preterm babies). Some literature looks at the incidence of BPD among all preterm babies with RDS; however, because gestational age is a critical determinant of this outcome, we had to adjust our estimates to be representative of the population of interest. Fortunately, it is clear that the probability of BPD given RDS follows an approximately logistic distribution with respect to birthweight (that is, the log-odds of BPD have a linear relationship with birthweight; Horbar et al. 2003) and the committee was content to assume that a similar relationship holds for gestational age.

Therefore, we were able to base our calculations on a prediction model for BPD by Zysman-Colman et al. (2013). We take 3 datapoints from this study: the prevalence of BPD among all premature babies with RDS is 36% (806 out of 2,233 cases), the mean gestational age is 31.2 weeks and the odds ratio for BPD per additional week of gestation is 0.62 (95%CI: 0.60 to 0.64). Using these data (and the assumption of a logistic relationship between gestational age and probability of BPD), we can estimate $o_{(\text{BPD}|\text{RDS},\, x)}$ – the odds that a child born with RDS at gestational age x will develop BPD:

$$o_{(\text{BPD}|\text{RDS},\, x)} = \frac{0.36}{1\text{-}0.36} 0.62^{(x\text{-}31.2)} \quad \textbf{(1)}$$

And then a standard odds-to-probability transformation gives us $p_{(\text{BPD}|\text{RDS},\, x)}$ – the probability a child with RDS born at gestational age x will develop BPD:

$$p_{(\text{BPD}|\text{RDS},\, x)} = \frac{o_{(\text{BPD}|\text{RDS},\, x)}}{1+o_{(\text{BPD}|\text{RDS},\, x)}} \quad \textbf{(2)}$$

By design, gestational age will be different in an immediate delivery strategy than with expectant management. Therefore, the probability that neonates experiencing RDS will go

on to develop BPD will also vary between the 2 approaches. To capture this, we used the mean gestational ages from Morris et al. (2016): mothers randomised to immediate delivery gave birth at an average of 35.1 week's gestation whereas, for the expectant management strategy, the equivalent value was 35.6 weeks. Plugging these numbers into equations (1) and (2) gives final estimates for the model: $p_{(\text{BPD}|\text{RDS},\ 35.1)}$ = 0.0798 for immediate delivery and $p_{(\text{BPD}|\text{RDS},\ 35.6)}$ =0.0635 for expectant management.

Caesarean section

The model assumes a baseline caesarean section probability of 30.1% for expectant management. This figure comes from NHS maternity statistics 2018–19, which reports 179,475 caesareans among 596,101 total deliveries for which mode of delivery is recorded. The included RCTs from the clinical review (Tajik et al. 2014; Morris et al. 2016) report a lower probability of caesarean deliveries in their expectant management arms. However, these trials report predominantly non-UK practice (Tajik et al. 2014 is Dutch; Morris et al. 2016 is international, with mostly Australian participants), and the committee advised that rates of caesarean section are highly dependent on prevailing practice in the country in question. Therefore, we use the NHS maternity statistics estimate – which has the advantage of being UK-specific but has the disadvantage of not being drawn from the subpopulation in which we are interested – for our base case, and explore the impact of the RCT-derived estimates in sensitivity analysis (see Table HE006).

Table HE006: Probability of caesarean section

	Risk
Base case	
NHS maternity statistics (2018–19)	30.1% (179,475/596,101)
Alternative value (scenario analysis)	
Morris et al. (2016)	18.5% (169/912)
Tajik et al. (2014) (GBS+ only)	15.2% (7/46)
Tajik et al. (2014) (GBS-)	15.0% (47/313)
Trial-arms pooled[a]	17.6%

(a) fixed-effect meta-analysis on log-odds scale

I.3.3.2 Long-term consequences

Risk of disability due to infection

The model assumes that infections may lead to long-term disability. We took the risks of disability due to infection from the same NIHR-funded evidence synthesis that was used to estimate sequelae in CG149 (Colbourn et al. 2007), as summarised in Table HE007. The analysis applies separate disability risks for meningitis and sepsis without meningitis.

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

	Risk of disability (95% CI)	
	Meningitis	Sepsis without meningitis
No disability	0.614 (0.535 to 0.692)	0.746 (0.641 to 0.838)
Mild disability	0.196 (0.136 to 0.264)	0.045 (0.011 to 0.100)
Moderate disability	0.129 (0.081 to 0.187)	0.139 (0.072 to 0.222)
Severe disability	0.061 (0.029 to 0.104)	0.070 (0.023 to 0.138)

Consequences of bronchopulmonary dysplasia (BPD)

The model assumes that the proportion of neonates who have RDS and go on to develop BPD are at risk of lifelong sequelae. The best source of evidence we identified for this was a Canadian case series reported by Landry et al. (2011), reviewing children with BPD after 2–5 years' follow-up. In their study, the 3 most prevalent complications are developmental delay, neurological impairment and wheezing episodes/asthma. Based on their clinical experience, the committee agreed that these were most relevant to our decision problem.

Landry et al. (2011) stratify risk of long-term complications according to BPD severity. However, the cohort is, on average, more premature than our model population (28 weeks versus 34+ weeks gestational age). The committee agreed that severe BPD is very seldom seen in late-preterm neonates so, in our base case, we assume that all cases of BPD are mild; we explore the impact of this assumption by using the risks across all severities of BPD in a scenario analysis. Table HE008 summarises the inputs.

Table HE008: Long-term complications related to BPD (from Landry et al. 2011)

	Mild BPD (base case)	All BPD (scenario analysis)
Developmental delay	34.3% (12/35)	52.4% (87/166)
Neurological impairment	14.3% (5/35)	20.4% (33/162)
Wheezing episodes/ asthma	35.9% (14/39)	34.3% (35/102)

NB denominators not specified in original article, but possible to infer from published event-counts and percentages

Consequences of caesarean sections for future pregnancies

Using ONS childbearing data, we calculate that 55% of live deliveries will have at least 1 subsequent live delivery. The mean number of expected future live deliveries, among women who have at least 1 more child, is 1.46. 14.3% of pregnancies will not result in a live birth post-caesarean (Table HE011); therefore, 1.704 pregnancies would occur to produce 1.46 live births.

In order to discount the costs of future pregnancies appropriately we also need to understand the expected length of time between pregnancies. ONS birth interval figures shown that the median birth interval is 35 months.

Table HE009: Expected future births

Expected future deliveries	Proportion of women	Median birth interval	Proportion of future births
1	100%	35	68%
2	36%	70	25%
3	10%	105	7%

By combining this with the number of future expected births (if>0), we can estimate the mean birth interval until a future delivery as:

$35 \times 0.68 + 70 \times 0.25 + 105 \times 0.07 = 48.5$ months

This is equal to 4.04 years.

Consequences of caesarean section for future pregnancies – additional caesareans

The clearest consequence of a caesarean section is that it substantially raises the chances that any future babies the mother has will also be delivered by caesarean. Data from the NHS Maternity Audit (2019) show that the rate of vaginal birth after caesarean (VBAC) is

24.9%; we use the complement of this value directly to estimate the probability of caesarean in all future births for women whose current baby is delivered by caesarean section. However, to quantify how much a caesarean in the current birth raises this probability, we also need to know what the probability of caesarean would have been if the current baby had not been delivered by caesarean section. We approximate this figure using data from NHS maternity statistics. We multiply the proportion of women who did not have a VBAC by the proportion of women who had a caesarean for their first delivery: 0.749 × 0.306 = 22.9%. We then assume that the remaining caesareans came from mothers who did not have a caesarean for their first child; see Table HE010.

Table HE010: Mode of delivery for subsequent pregnancies

Type	Value	Source / derivation
VBAC (a)	25.1% (12,449/49,542)	Maternity Audit 2019 (England)
Primiparous caesareans (b)	30.6% (46,839/153,279)	NHS maternity statistics (2018–19)
Multiparous caesareans (c)	30.3% (39,240/129,364)	NHS maternity statistics (2018–19)
As proportion of multiparous births		
Caesarean after caesarean (d)	22.9%	b × (1−a)
Caesarean after non-caesarean (e)	7.5%	c−d
Non-caesarean after caesarean	7.7%	b × a
Non-caesarean after non-caesarean	62.0%	(1−b)−e
Probabilities		
Caesarean given prior caesarean	0.749	1−a
Caesarean given no prior caesarean	0.107	(c−d) / (1−b)

Consequences of caesarean section for future pregnancies – adverse outcomes

The model also uses evidence that women who have had a caesarean section are at higher risk of ectopic pregnancy, miscarriage or stillbirth in future pregnancies, based on a published meta-analysis (Keag et al. 2018).

The model applies these relative effects to estimates of absolute risk of each event drawn from the literature:

- 1.1% for ectopic pregnancy; following NICE NG126, we draw this estimate from a 3-year review of adverse pregnancy events in Britain and Ireland (Lewis et al. 2007).
- 12.8% for miscarriage, based on a large, recent cohort study from Norway (Magnus et al., 2019).
- 4.1 stillbirths per 1,000 total births in England, based on ONS 2017 data.

However, each of these absolute risks represents a mixture of women who have not undergone a previous caesarean section and those who have. We need to adjust for this to arrive at a best estimate of event-rates with and without the exposure. We do this using 3 pieces of information: the observed probability in all women (which we convert to odds), the odds ratio for exposed -v- unexposed, and an estimate of the proportion of women who have the exposure. From the NHS maternity statistics 2018–19, we estimate that approximately one-fifth of pregnant women have a history of caesarean section (82,949 ÷ 426,698 = 19.4%; 82,949 = [421,552 births − 153,279 to exclude primiparous] × 0.306 [b in Table HE010]).

Using these 3 values, we note that the observed odds of experiencing the event (o_{all}) are a combination of the odds with the exposure (o_{CS}) and odds without the exposure (o_{noCS}) weighted according to the probability of exposure (p_{CS}):

$$o_{all} = o_{CS}p_{CS} + o_{noCS}(1 - p_{CS}) \quad \textbf{(3)}$$

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

$$o_{CS} = o_{noCS}OR_{CS\text{-}v\text{-}noCS} \quad \textbf{(4)}$$

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

$$o_{noCS} = \frac{o_{all}}{(1 - p_{CS}) + p_{CS}OR_{CS\text{-}v\text{-}noCS}} \quad \textbf{(5)}$$

Once we have a result for the unexposed, we plug it into equation (4) to estimate odds in the exposed. Finally, we convert the resulting odds to probabilities. The results of these calculations are shown in Table HE011.

Table HE011: Future pregnancy events

Event	Baseline probability	Source	Odds ratio prev. caesarean -v- none (95%CI)	Source	Probability according to prev. caesarean	
					No	Yes
Miscarriage	12.8% (53,906 / 421,201)	Magnus et al. (2019)	1.21 (1.04 to 1.40)	Keag et al. (2018)	12.4%	14.6%
Ectopic	1.1% (32,100 / 2,891,892)	Lewis et al. (2007)	1.17 (1.03 to 1.32)	Keag et al. (2018)	1.07%	1.26%
Stillbirth	0.41% (2,689 / 659,765)	ONS 2018	1.27 (1.15 to 1.40)	Keag et al. (2018)	0.39%	0.49%

I.3.3.3 Mortality

The model accounts for mortality risks related to acute events: infection (subdivided into meningitis and sepsis) and BPD. We also need an estimate of expected lifespan to estimate the costs and effects for neonates sustaining lifelong morbidity.

Death from neonatal meningitis

To predict the likelihood of death in neonates who contract meningitis, the model uses data from a surveillance cohort in the UK and Ireland (Okike et al. 2014). This evidence shows that risk of death is strongly associated with gestational age. Therefore, we calculate separate case-fatality rates for our 2 cohorts, using the proportion of babies born at less than 37 weeks' gestational age from Morris et al. (2016). This leads to a somewhat higher risk of death in the immediate delivery arm, in which almost all neonates were born prematurely, than in the expectant management arm, where some babies reached term.

Previous analyses (including CG149) have used data from Colbourn et al.'s multiparameter evidence synthesis (2007) to estimate this parameter. We explore the use of these alternative values in sensitivity analysis. The study estimates case-fatality probabilities for both term and preterm babies; however, in this case, preterm cases include very premature babies that are outside our decision-space. Therefore, the committee advised that it would be most appropriate to use estimates for term babies alone.

Table HE012: Death from neonatal meningitis

	Risk of death	Source
Base case		
32–36 weeks' gestation	9.3% (4/43)	Okike et al. (2014) Tab 3
37+ weeks' gestation	4.3% (10/235)	Okike et al. (2014) Tab 3
Weighted average for each approach:		
Immediate (96.9% <37wk)	9.1%	
Expectant (79.4% <37wk)	8.3%	
Alternative value (scenario analysis)		
Early onset GBS meningitis term	0.124 (95%CI: 0.027 to 0.277)	Colbourn et al. (2007) Tab 26
Late onset GBS meningitis term	0.111 (95%CI: 0.037 to 0.216)	Colbourn et al. (2007) Tab 26

Death from neonatal sepsis

We used a similar approach to estimate the probability of death from sepsis without meningitis. Data from the same surveillance unit (O'Sullivan et al. 2019) provide outcome data for 856 cases of invasive GBS that was predominantly classified as sepsis. As for meningitis, risk of death is strongly associated with gestational age, and we account for this in the same way, by weighting gestation-specific risks by probability of preterm birth in each arm (see Table HE013).

However, this study also includes a small proportion of neonates with GBS-related meningitis (57 of 517 cases with 3 of 27 deaths), which we would ideally like to exclude from this model parameter, and only presents gestation-stratified case-fatality results in this mixed cohort. We are able to exclude the cases from the overall death-rate, though we are not able to account for gestational age if we do so, so we include a single fatality-rate for both arms as a sensitivity analysis. In addition, we explore the data from Colbourn et al. (2007), as before.

Table HE013: Death from neonatal sepsis

	Risk of death	Source
Base case		
34–36 weeks' gestation	6.1% (3/49)	O'Sullivan et al. (2019)
37+ weeks' gestation	2.7% (9/330)	O'Sullivan et al. (2019)
Weighted average for each approach:		
Immediate (96.9% <37wk)	6.0%	
Expectant (79.4% <37wk)	5.4%	
Alternative value (scenario analysis)		
All gestational ages, no meningitis	5.2% (24/460)	O'Sullivan et al. (2019)
Early onset GBS sepsis term	0.053 (95%CI: 0.025 to 0.088)	Colbourn et al. (2007) Tab 26
Late onset GBS sepsis term	0.061 (95%CI: 0.012 to 0.141)	Colbourn et al. (2007) Tab 26

Death related to BPD

The model also captures the additional mortality associated with BPD. As described above, the committee preferred to assume that all cases of BPD are mild in our base-case model. Landry et al. (2011) reported a mortality risk of 2% (1/60) among mild BPD patients. We test this in sensitivity analysis using data on all severities of BPD from the same study (noting that this includes a large proportion of infants who were born much more prematurely than our cohort): 16.5% (53/322).

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 HE014 shows the resulting estimates.

Table HE014: Expected lifespan of neonatal survivors

Severity of impairment	Hazard ratio (95%CI) (Reid et al. 2012)	Equivalent life expectancy at birth (using 2016–18 UK lifetables; ONS 2019)		
		Undiscounted	Discounted	
			3.5% / year	1.5% / year
Motor impairment				
None		81.04	27.40	46.89
Mild	1.00	81.04	27.40	46.89
Moderate	1.51 (0.71 to 3.24)	76.82	27.02	45.48
Severe	6.21 (3.28 to 11.77)	60.59	24.87	39.13
Intellectual impairment				
None	1.00	81.04	27.40	46.89
Mild–moderate	1.11 (0.62 to 1.97)	79.98	27.31	46.55
Severe–profound	3.01 (1.74 to 5.22)	69.29	26.17	42.73

I.3.4 Treatment effects

Our primary source of treatment effects is the systematic review undertaken for this review (see above), which focused exclusively on the population specified in the review question (that is, women with PPROM and GBS detection). However, a critical question for our model is whether it is always better to rely on the relatively limited amount of data available from this review or consider the somewhat richer dataset describing all randomised women with PPROM. Each of the included RCTs enrolled women regardless of GBS status, and reports the GBS-positive subgroup for some outcomes. Additionally, several other RCTs were excluded from the review because they do not report results stratified according to GBS status. These are collected in a Cochrane review (Bonds et al. 2017).

The committee advised that, for some outcomes, GBS status will be a key determinant of relative effect whereas, for others, it is reasonable to assume that it has minimal impact on results. Therefore, relying on the committee's expertise, we selected the most appropriate dataset for each of the 3 outcomes on a case-by-case basis. Where the committee preferred the broader dataset, we used the estimate from the Cochrane review (Bonds et al. 2017) – if we are content to broaden our eligibility criteria for a parameter, we should use the largest sample of data available. However, we present the equivalent results from the full populations of the included RCTs for comparative purposes.

To test the impact of this decision-making, we also performed a scenario analysis adopting a strict interpretation of the PICO – that is, restricting all 3 relative effectiveness inputs to the subpopulation of GBS-positive women only.

Both the clinical review for this chapter and the Cochrane review present their results as relative risks. It is mathematically convenient for our model to work on an odds scale, so we calculated the equivalent odds ratios for each, using the same models adopted in the original syntheses.

I.3.4.1 Infection

For risk of infection, the committee was positive that our estimate of relative effect should come from the population directly reflecting our decision problem: that is, women with preterm, prelabour rupture of membranes with GBS detection. Therefore, we took this value from the clinical review (see above), which showed that expectant management is associated with a relative risk of infection of 2.73 (95%CI: 0.34 to 22.18) compared with immediate delivery. The equivalent odds ratio is 2.93 (95%CI: 0.33 to 26.19). Because the committee was clear that it would not be appropriate to use infection rates from women without GBS detection, we do not use those data even for sensitivity analyses.

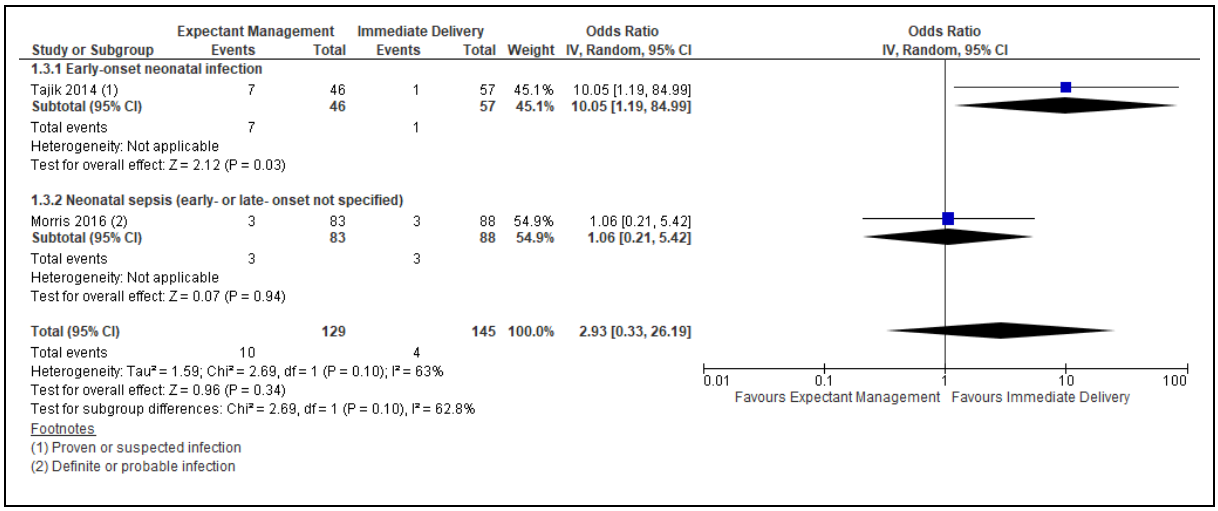


Figure HE002: Treatment effects (expectant management -v- immediate delivery): infection

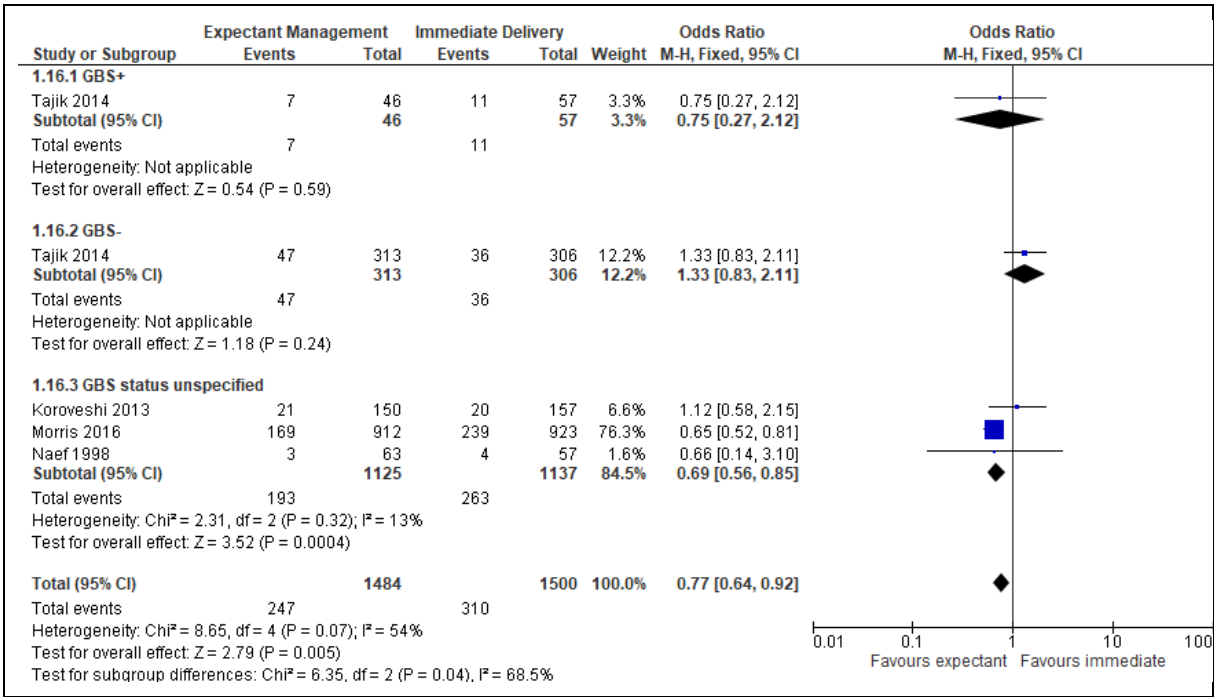
Table HE015: Treatment effects (expectant management -v- immediate delivery): infection

	GBS status	N RCTs	Odds ratio (95%CI)	I^2	Model
Included RCTs (base case)	**GBS+ only**	**2**	**2.93 (0.33 to 26.19)**	**63%**	**RE**
Included RCTs	All	not appropriate for this outcome			
Cochrane review	All				

I.3.4.2 Caesarean section

For probability of caesarean section, the committee advised that the mother's GBS status is likely to have minimal impact. Therefore, in our base case, we use data from the 5 RCTs pooled in the Cochrane review.

Figure HE003 shows a stratified forest plot for the analysis. There is a degree of heterogeneity between results, with the 1 exclusively GBS-negative datapoint appearing to show a different pattern. However, the pooled total is closely comparable with the estimate from the GBS-positive subgroup of the 1 RCT that stratifies results (Tajik et al. 2014). Therefore, at the point estimate, it makes little difference which dataset we use, although uncertainty is obviously reduced in the bigger sample.



Note that the pooled total in this graph is very slightly different from the estimate from the Cochrane review we use in our model because it shows GBS-stratified results from Tajik et al. (2014), to explore evidence for GBS-related heterogeneity, whereas the Cochrane review uses data from the main publications from the same trial (Van der Ham et al. 2012a, 2012b), which include a few more participants with undetermined GBS status.

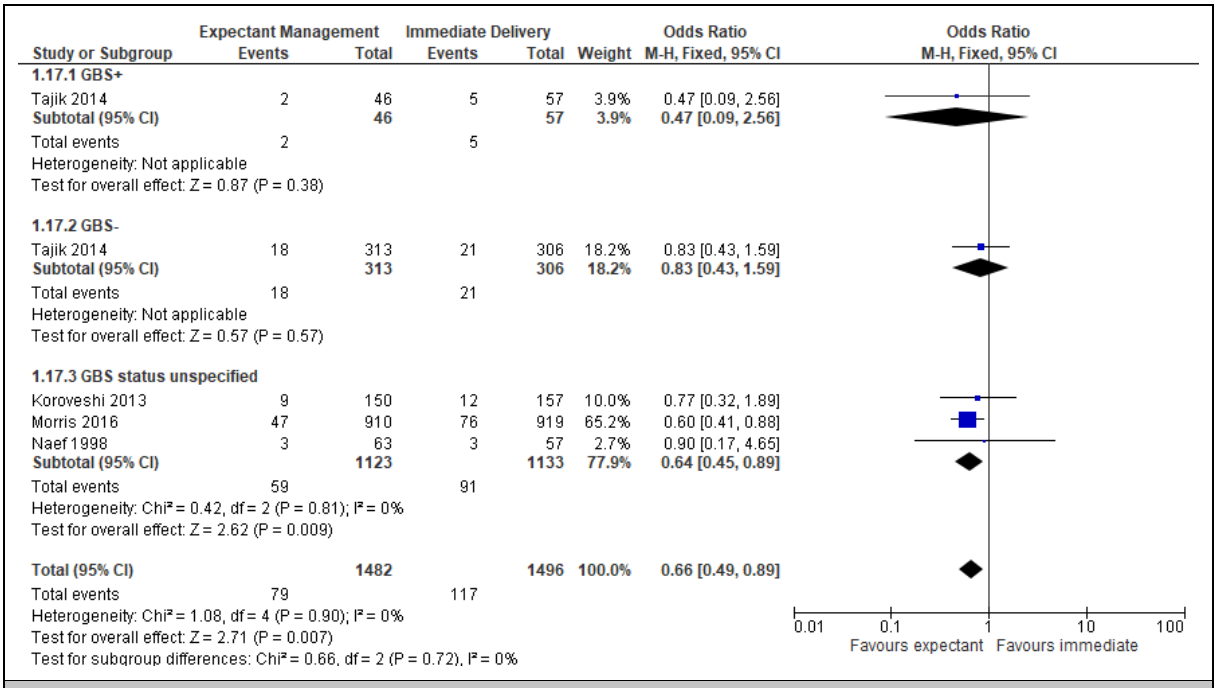
Figure HE003: Treatment effects (expectant management -v- immediate delivery): caesarean section

Table HE016: Treatment effects (expectant management -v- immediate delivery): caesarean section

	GBS status	N RCTs	Odds ratio (95%CI)	I^2	Model
Included RCTs	GBS+ only	1	0.75 (0.27 to 2.12)	NA	NA
Included RCTs	All	3	0.86 (0.50 to 1.48)	73%	RE
Cochrane review (base case)	**All**	**5**	**0.78 (0.65 to 0.94)**	**62%**	**FE**

I.3.4.3 Risk of respiratory distress syndrome (RDS)

For risk of RDS, the committee was again content to pool evidence from GBS-positive women with data from groups in which GBS status was negative or unknown. Results are shown in Figure HE004. Here, there is a good degree of agreement between the datapoints, all of which show that immediate delivery is associated with higher rates of RDS, regardless of mothers' GBS status.



Note that the pooled total in this graph is very slightly different from the estimate from the Cochrane review we use in our model because it shows GBS-stratified results from Tajik et al. (2014), to explore evidence for GBS-related heterogeneity, whereas the Cochrane review uses data from the main publications from the same trial (Van der Ham et al. 2012a, 2012b), which include a few more participants with undetermined GBS status.

Figure HE004: Treatment effects (expectant management -v- immediate delivery): respiratory distress syndrome

Table HE017: Treatment effects (expectant management -v- immediate delivery): respiratory distress syndrome

	GBS status	N RCTs	Odds ratio (95%CI)	I^2	Model
Included RCTs	GBS+ only	1	0.47 (0.09 to 2.56)	NA	NA
Included RCTs	All	3	0.64 (0.47 to 0.89)	0%	FE
Cochrane review (base case)	**All**	**5**	**0.67 (0.50 to 0.90)**	**0%**	**FE**

I.3.5 Quality of life

The model estimates QALYs for both mothers and babies. For the mothers, we present utility as QALY decrements, as the interventions themselves only have a short-term impact on the mothers and subsequent long-term expectations would cancel out between arms. The QALYs for the babies 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 the model applies is based on age-adjusted EQ-5D data for UK general population (Kind et al. 1999).

The model does not treat the sequelae of acute neonatal events as mutually exclusive. For example – although the proportion is very small, arising as the product of multiple small probabilities – a nonzero proportion of the cohort experience both disability following neonatal infection and RDS leading to BPD and consequent morbidity. In such cases, we combine disutilities following a validated multiplicative approach (Ara and Wailoo, 2012).

To derive the condition-specific utility values for the model health states and adverse events, a multiplier (M_A) is estimated based on the proportional difference between the health condition utility (U_A) and the utility of people without the condition (U_{nA}):

$$M_A = U_A / U_{nA}$$

The model then uses the multiplicative approach to combine more than 1 utility multiplier:

$$M_{A.B} = M_A \times M_B$$

The model applies the combined multipliers to the baseline utility to estimate the utility of babies in the model.

I.3.5.1 Utility associated with infections and their consequences

The model does not account for QALY loss 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 their quality of life. 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 a woman in the UK aged 25–34 (Dolan 1995). 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.

The model 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.

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 estimate accurately the impacts on the family in instances of events such as neonatal death.

I.3.5.2 Utility associated with long-term consequences of infection

We use the same HRQoL values for the long-term consequences of both meningitis and sepsis; that is, although we make use of evidence suggesting that the risk of sequelae is different for meningitis and sepsis, and the severity of impact also varies between the 2 (see

I.3.3.2), the model treats, e.g., 'moderate neurological impairment' caused in either way as the same.

Previous analyses (including Colbourn et al. 2007 and CG149) have accounted for long-term neurological impairment 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.3.5.3 Utility associated with BPD and its consequences

The model assumes no direct QALY loss due to RDS, for the same reasons we do not account for the immediate impact of infections. However, as described in I.3.3.2, the model simulates a proportion of babies with RDS will be categorised as having BPD, a proportion of whom will, in turn, experience lifelong sequela(e).

For the proportion of people experiencing asthma / wheezing, we draw our estimate of disutility from an extensive analysis of data from the English General Practice Patient Survey 2011–2012 (Mujica-Mota et al., 2015), including 102,070 out of 906,578 (10.8%) respondents reporting 'Asthma or long-term chest problem'. In a multivariable analysis adjusting for sociodemographic factors and the presence of many other conditions, the authors estimate the independent effect of asthma to be associated with a disutility of −0.058 (95%CI: −0.063 to −0.053) against a background expected utility value of 0.933 (95%CI 0.932 to 0.935) for people with no chronic health conditions. However, asthma is a common condition and, because we want to estimate the sequelae of BPD over and above what

would be expected for people not experiencing it, we adjust general population utility to reflect the proportion of people who have asthma: 0.933 − 0.053 × 0.108 = 0.927. This gives us a final utility multiplier of (0.933 − 0.053) ÷ 0.927 = 0.944.

For neurodevelopmental sequelae of BPD, we use the same evidence we use for infection (see Table HE018). However, the datasource we use to estimate the likelihood of BPD sequelae (Landry et al. 2012; see I.3.3.2) distinguishes between 'developmental delay' and 'neurological impairment', whereas our utility values reflect a single, broader category incorporating the 2. Therefore, the model assumes that 'developmental delay' equates to 'mild neurodevelopmental impairment' (utility multiplier 0.813), 'neurological impairment' equates to 'moderate neurodevelopmental impairment' (utility multiplier 0.689), and experiencing both 'developmental delay' and 'neurological impairment' equates to 'severe neurodevelopmental impairment' (utility multiplier 0.418). As a sensitivity analysis, we use a weighted average of all 3 categories – weighted according to the proportions reported by Petrou et al. (117/57/22 mild/moderate/severe) – for both outcomes.

I.3.5.4 Consequences of caesarean sections for future pregnancies

The model assumes caesarean delivery is associated with a negative impact on QALYs from an increased risk of ectopic pregnancy, miscarriage and stillbirth in future pregnancies.

The model assumes miscarriage is associated with an absolute decrement of 0.1 QALYs. This replicates the assumption used in NICE's guideline on ectopic pregnancy and miscarriage (NG126). However, it should be noted that there is no empirical basis to the value; rather, it was used as a starting-point for a range of sensitivity analyses in the absence of an evidence-based parameter. Similarly, we did not identify a suitable source for utility decrement of ectopic pregnancy, so we assume it has the same QALY impact as miscarriage, and test a broad range of values in sensitivity analysis.

For each stillbirth, the model subtracts an expected lifetime's discounted QALYs to reflect the loss of a life (25.08 QALYs when discounted at 3.5% per year). While we acknowledge that this event will also have a profound impact on the child's parents, we did not identify any suitable sources to help us quantify this effect. In discussion with the committee, we agreed that any attempt to approximate the true impact would be inadequate, and it is better simply to note this as a limitation of our analysis.

I.3.6 Cost and healthcare resource-use

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 above). 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.

- 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.3.6.1 Direct costs of interventions

To account for the direct costs of the 2 strategies, we estimate costs in 3 categories: antenatal care, delivery and neonatal care. As a matter of principle, we would expect expectant management to be associated with higher antenatal costs (because mothers remain pregnant for longer) and we would expect immediate delivery to be associated with higher neonatal costs (because babies will be born more prematurely). Differences in delivery costs are largely a function of the proportion of expected caesarean sections: in view of the evidence that expectant management is associated with fewer caesareans (see I.3.4.2), we would expect that approach to have lower average delivery costs.

For all 3 categories, a potentially valuable source is Lain et al.'s economic evaluation (2017) accompanying the PPROMT RCT (Morris et al. 2016). This study provides detailed information on resource-use and total costs observed in people randomised to the 2 approaches in which we are interested. However, there are some aspects of the study that make it suboptimal, for our purposes: (a) data are only available for the whole trial population, whereas we are only interested in the subgroup of women with GBS detection, who may have different patterns of resource-use; (b) PPROMT was an international trial, and both resource-use and costs will differ between countries – for example, there will be higher or lower prevailing rates of caesarean sections compared with vaginal births, and different unit costs for each (the evaluation uses a mixture of UK and Australian costs); we are only interested in UK practice and costs; (c) even where UK unit costs are used in the analysis, they are drawn from the 2011/12 NHS Reference Costs; obviously, we would prefer current costs and, while historical costs can be inflated using standard sources, this only provides an approximation of present-day values.

On committee advice, we concluded that issue (a) will not be especially problematic for antenatal or delivery costs – that is, women with prior detection of GBS will not have meaningfully different antenatal or delivery costs following rupture of membranes. Therefore, we use data from Lain et al.'s whole randomised cohort to represent our population of interest. However, when it comes to neonatal costs, the potential for differential incidence of infections in the GBS+ subgroup may have important consequences, so we make some adjustments to our estimates to account for this (see below). In response to problems (b) and (c), we explore 2 alternative approaches to estimating costs. Our base case takes a microcosting approach, using resource-use estimates from Lain et al. (2017) and applying current unit costs to estimate totals. In a scenario analysis, we use Lain et al.'s totals directly, inflating them from 2011/12 to 2018/19 using HCHS/NHSCII inflators (PSSRU 2019).

I.3.6.2 Antenatal care

The categories of antenatal care the model accounts for are those enumerated by Lain et al. (2017): inpatient admissions, day cases and outpatient appointments. Unit costs for these categories (taken from NHS Reference Costs 2016/17 and subsequently inflated; see below) are shown in Table HE019 and Table HE020.

Table HE019: Unit costs (2016/17) for antenatal care – inpatient admissions

Code	Nonelective admissions				Excess bed-days		Average		Weighted average per day
	Mean (SE[a])	Subm-issions	Epi-sodes	Mean LoS (d)	Mean (SE[a])	N	Per episode	Per day	
NZ17A[b]	£1,953 (£45)	213	1,747	2.47	£425 (£21)	1,486	£2,314	£698	£677.58
NZ17B[c]	£1,719 (£26)	394	7,651	2.40	£512 (£13)	4,841	£2,043	£673	

(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) Ante-Natal False Labour, including Premature Rupture of Membranes, with CC Score 2+
(c) Ante-Natal False Labour, including Premature Rupture of Membranes, with CC Score 0-1

Table HE020: Unit costs (2016/17) for antenatal care – day cases and outpatient appointments

Category	Code	Mean (SE[a])	Subm-issions	Epi-sodes	Weighted average
Day cases	NZ17A[b]	£292 (£52)	8	52	£278.03
	NZ17B[c]	£278 (£4)	31	1,877	
Outpatient appointments	WF01A[d] (501 Obstetrics)	£120 (£5)	134	1,539,008	£120.20

(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) Ante-Natal False Labour, including Premature Rupture of Membranes, with CC Score 2+
(c) Ante-Natal False Labour, including Premature Rupture of Membranes, with CC Score 0-1
(d) Non-Admitted Face-to-Face Attendance, Follow-up

We use these costs to value the resource-use observed in PPROMT (Lain et al. 2017), as shown in Table HE021, which also shows values for the scenario analysis relying directly on total costs from the same publication. As expected, expectant management is associated with greater antenatal expenditure, with the difference between the 2 approaches amounting to somewhere in the region of £1,450–£1,650, depending on costing approach.

Table HE021: Cost calculations for antenatal care

Strategy	Resource-use – mean (SE) (from Lain et al. 2017)			Total costs	Inflated to 2018/19
	Inpatient days	Day cases	Outpatient appts		
Base case – microcosting					
Immediate delivery	1.09 (0.05)	0.09 (0.03)	0.06 (0.02)	£770.79[a]	£797.75
Expectant management	3.27 (0.14)	0.49 (0.06)	0.17 (0.03)	£2,372.35[a]	£2,455.30
Scenario analysis – total costs from Lain et al. (2017)					
Immediate delivery	–	–	–	£724.00[b]	£804.17
Expectant management	–	–	–	£2,046.00[b]	£2,272.56

(a) Cost year = 2016/17
(b) Cost year = 2011/12

I.3.6.3 Delivery costs

The costs associated with delivery are a simple function of the expected balance of caesarean sections and non-caesarean delivery. For the unit costs of non-caesarean delivery, we use a weighted average of all vaginal (including instrumental) delivery codes in the NHS Reference Costs. This set comprises 30 HRGs: NZ30A–C, NZ31A–C, NZ32A–C,

NZ33A–C, NZ34A–C, NZ40A–C, NZ41A–C, NZ42A–C, NZ43A–C and NZ44A–C. We include costs recorded under the following categories: elective (including excess bed-days), nonelective (including excess bed-days), nonelective short stay, day case, and community health services. In total, this amounts to 461,590 episodes across 210 category–HRG codes. For brevity, we do not reproduce each individual cost estimate here, but each is included in the model along with an estimate of its standard error (calculated as noted in Table HE019); in probabilistic mode, the model calculates an average (weighted according to activity) of sampled values for all codes. The deterministic mean is £2,478.58 which, when uprated from 2016/17, equates to £2,565.25 in 2018/19 value.

Similarly, caesarean section unit costs are calculated as a weighted average of values recorded under HRGs NZ50A–C (planned) and NZ51A–C (emergency), with elective (including excess bed-days), nonelective (including excess bed-days), nonelective short stays and day cases included. Table HE022 shows the mean values derived in this way.

Table HE022: Unit costs for caesarean sections

Type	Codes	Episodes	Mean (2016/17 values)	Inflated to 2018/19
Planned	NZ50A–C	74,652	£3,557.42	£3,681.81
Emergency	NZ51A–C	97,979	£4,780.59	£4,947.76
Planned + emergency		172,631	£4,251.65	£4,400.32

For costing purposes, we split caesarean deliveries into 2 categories: those that would be expected (see I.3.3.1), and excess events arising as a result of the chosen mode of management. The evidence we use in the model suggests that immediate delivery is most likely to be associated with more caesareans (see I.3.4.2) though, in any given iteration of the probabilistic model, it is possible that an OR>1 will be sampled, implying expectant management leads to more caesareans. For the expected events (the caesarean sections that would have happened one way or another), we assume the procedures are a mixture of planned and emergency procedures, in the same proportions observed in the general population. For the excess events (the caesarean sections that result from the chosen mode of managing the PPROM), we assume all procedures would be coded as emergencies. Table HE023 shows the base-case calculations, alongside values for the scenario analysis relying directly on total costs from Lain et al. (2017). The 2 approaches reach similar conclusions, with immediate delivery associated with a small increase in costs in the range £133–£212.

Table HE023: Cost calculations for delivery

Strategy	Proportions			Total costs	Inflated to 2018/19
	Expected caesareans (planned & emergency)	Excess caesareans (emergency)	Non-caesareans		
Base case – microcosting					
Immediate delivery	0.301	0.056	0.643	£3,140.75[a]	£3,250.58
Expectant management	0.301	–	0.699	£3,012.42[a]	£3,117.76
Scenario analysis – total costs from Lain et al. (2017)					
Immediate delivery	–	–	–	£2,867.00[b]	£3,184.48
Expectant management	–	–	–	£2,676.00[b]	£2,972.33

(a) Cost year = 2016/17
(b) Cost year = 2011/12

I.3.6.4 Neonatal costs

The costs associated with hospital care for the newborn baby will be substantially affected by the incidence of infections. As noted in I.3.4.1, the committee was clear that, when it comes to infections, we should only use evidence from trial subgroups that reflect our population of interest – that is, women with prior detection of GBS. As a result, the expected rate of neonatal infections in our model is quite different from that observed in the overall trial populations, both in absolute (see I.3.3.1) and relative (see I.3.4.1) terms. For this reason, it would not be appropriate to use resource-use or total cost estimates from Lain et al. (2017) directly, as they represent the rate of infections observed in the overall RCT population, regardless of the mothers' GBS status.

To address this problem, we adopt a relatively simple 4-stage approach that aims to disaggregate costs directly associated with infections and other neonatal care costs. (1) We calculate the costs observed in the full PPROMT population (Lain et al. 2017), in the same way as for the previous categories of perinatal costs. (2) We estimate the additional costs associated with an average neonatal infection, compared with a baby who does not experience this event. (3) We multiply the cost by the infection rate observed in the full trial population of PPROMT, and deduct those costs from the estimate calculated in step (1), to provide an estimate of the resource-use and costs that would be expected if none of the neonates had experienced an infection. (4) We multiply our estimate of infection costs by the rates of infections we expect in each modelled arm of our GBS+ population, and add those back on to our estimate of costs without infections, to provide an estimate of the resource-use and costs that corresponds to the rate of infections in the model.

Table HE024 shows the daily costs we use for all these calculations. Where we require a unit cost for critical care without further specification as to level of support, we use an activity-weighted average of codes XA01Z–XA04Z. This amounts to £721.44 per day.

Table HE024: Unit costs (per day) for neonatal care

Code	Submissions	Days	Mean cost per day (SE[a])[b]	Inflated to 2018/19
XA01Z[c]	129	159,664	£1,295 (£34)	£1,340
XA02Z[d]	129	183,555	£897 (£18)	£929
XA03Z[e]	129	535,683	£577 (£15)	£597
XA04Z[f]	106	152,758	£418 (£19)	£432
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 HE025 shows the calculation of neonatal costs for the (step (1) as explained above).

There is a larger difference between the 2 approaches than in previous categories. We speculate this may be because we have a single cost category, costed as a weighted average of codes XA01Z–XA04Z, for all days of critical care. However, it is plausible that the immediate delivery arm, which had a greater proportion of critical care and a greater duration of critical care than the expectant delivery arm, also featured a greater proportion of the most intensive, expensive critical care within that category. It is not possible for us to account for this using the data available to us.

Table HE025: Cost calculations for neonatal care as observed in overall trial population (regardless of mothers' GBS status)

Strategy	Critical care				Mean overall LoS in hospital – d (SE)	Postnatal ward – d[c]	Total cost	Inflated to 2018/19
	% admitted	Mean stay – d (SE)[a]	Mean stay per patient – d[b]	Cost				
Base case – microcosting								
Immediate	68.5% (631/921)	8.9 (0.3)	6.1	£4,538	7.4 (0.2)	1.3	£4,953[d]	£5,126
Expectant	59.1% (537/908)	7.8 (0.3)	4.6	£3,453	6.4 (0.2)	1.8	£4,101[d]	£4,244
Scenario analysis – total costs from Lain et al. (2017)								
Immediate	–	–	–	–	–	–	£5,261[e]	£5,844
Expectant	–	–	–	–	–	–	£4,022[e]	£4,467

(a) Mean stay among those admitted to critical care
(b) Mean stay in critical care for the average patient (i.e. probability of admission × mean stay among those admitted)
(c) Overall LoS minus critical care
(d) Cost year = 2016/17
(e) Cost year = 2011/12

Table HE026 sets out the calculations for step (2) of our process: estimating the excess resource-use and costs associated with neonatal infections. Our estimates are based on a prospective cohort study of infants with GBS disease in England (Schroeder et al. 2009). This study provides detailed data on resource-use for 138 infants (<90 days) experiencing early- or late-onset GBS infection, compared with 305 contemporaneous controls (matched for birthweight) who had no clinically evident infections. This is an ideal datasource for our analysis, with the single shortcoming that it reports relatively historical practice (2000–03).

Table HE026: Cost calculations for infections

Outcome	Days – mean (SE) (from Schroeder et al. 2009)				Total costs	Inflated to 2018/19
	NICU	HDU	SCU	Postnatal		
Base case – microcosting						
Infections	3.8 (0.9)	3.8 (0.6)	10.4 (1.1)	0.5 (0.3)	£14,174[a]	£14,669
Controls	1.9 (0.5)	1.4 (0.3)	4.6 (0.6)	2.0 (0.1)	£7,054[a]	£7,301
Difference	1.9	2.4	5.8	−1.5	£7,120[a]	£7,369
Scenario analysis – total costs from Schroeder et al. (2009)						
Difference	–	–	–	–	£5,209 (£1,286[b])[c]	£6,543

(a) Cost year = 2016/17
(b) Calculated from published bootstrapped 95% confidence interval (£2,843.3 to £7,885.80)
(c) Cost year = 2003

The final calculations, using the outputs of the 2 previous steps and performing steps (3) and (4), appear in Table HE027. The inclusion of expected costs of infection attenuates the advantage expectant management would otherwise have over immediate delivery in this area. Nevertheless, immediate delivery, with its higher proportion of premature babies, remains the more expensive approach, with an additional cost per baby of £237–£731, depending on the approach we use.

Table HE027: Final cost calculations for neonatal care

Strategy	Whole RCT population				GBS+ population		
	Total costs	Observed infections	Deduct cost of infections	Costs with no infections	Expected infections[a]	Costs of infections	Final estimate
Base case – microcosting							
Immediate	£5,126	2.5% (23/923)	−£184	£4,942	5.8%	£426	£5,368
Expectant	£4,244	3.2% (29/912)	−£234	£4,010	15.2%	£1,121	£5,131
Scenario analysis – total costs from Lain et al. (2017)							
Immediate	£5,844	2.5% (23/923)	−£184	£5,660	5.8%	£426	£6,086
Expectant	£4,467	3.2% (29/912)	−£234	£4,233	15.2%	£1,121	£5,354

(a) See I.3.3.1 for baseline probability with expectant management and I.3.4.1 for relative effect used to calculate expected event-rate for immediate delivery

The other major neonatal event our model accounts for (in terms of outcomes) is RDS. However, it is not necessary to cost these events separately in a similar way to infections. Committee advice was that a mother's GBS status is unlikely to have a meaningful effect on the likelihood of RDS, and the data bear this out as regards both absolute (I.3.3.1) and relative (I.3.4.3) event-rates. Notably, the estimates from PPROMT (Morris et al. 2016) are typical of the overall dataset and closely comparable with the values from the 1 GBS+ subgroup for which we have data (Tajik et al. 2014). Therefore, we have some confidence that the resource-use data from the same trial (Lain et al. 2017) reflects a level of RDS that closely corresponds to the expectation in our modelled population.

I.3.6.5 Total perinatal costs

Table HE028 summarises the results of calculations across all 3 categories of perinatal care. Expectant management appears to be the more expensive approach, mostly as a result of increased antenatal costs. The size of the estimated difference depends on costing approach, with the largest discrepancy arising in neonatal care costs, as discussed above.

Table HE028: Total perinatal costs

Category	Immediate delivery	Expectant management	Difference
Base case – microcosting			
Antenatal	£797.75	£2,455.30	−£1,657.56
Delivery	£3,250.58	£3,117.76	£132.82
Neonatal	£5,367.93	£5,130.94	£236.99
Total	**£9,416.25**	**£10,704.00**	**−£1,287.74**
Scenario analysis – total costs from Lain et al. (2017)			
Antenatal	£804.17	£2,272.56	−£1,468.39
Delivery	£3,184.48	£2,972.33	£212.15
Neonatal	£6,085.73	£5,354.39	£731.34
Total	**£10,074.38**	**£10,599.28**	**−£524.90**

I.3.6.6 Costs associated with disability due to infection

As detailed in I.3.3.2, we account for lifelong neurodevelopmental morbidity secondary to neonatal infection. The model subdivides cases into mild, moderate and severe impairment, with the relative prevalence of each depending on whether the person experienced meningitis or sepsis as a neonate.

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. Their major limitation, from our perspective, is that the cohort in question were all born at 20–25 completed weeks' gestation, much more prematurely than our population of interest. However, although the incidence of neurodevelopmental disability is higher in this population (and the proportion experiencing more severe impairment may also be raised), there is no reason to believe that children classified as having mild, moderate or severe impairment will have meaningfully different prospects to those experiencing mild, moderate or severe impairment in the less premature population in which we are interested. 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 HE029 provides details.

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).

Table HE029: 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	**–**	**£347.88**	**£405.46**	**£1,047.16**
Additional NHS+PSS costs of disability	–	£296.00[b]	£345.00[b]	£891.00[b]
Inflated from 2005/06 to 2018/19	–	£347.88	£405.46	£1,047.16
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	**–**	**£347.88**	**£1,583.08**	**£10,485.67**
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	–	£38.20	£173.81	£1,151.28
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)
(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

I.3.6.7 Costs associated with disability due to BPD

As for utilities (see I.3.5.3), we assume that 'developmental delay' as a consequence of BPD equates to 'mild neurodevelopmental impairment', 'neurological impairment' equates to 'moderate neurodevelopmental impairment', and a combination of the 2 equates to 'severe neurodevelopmental impairment' and use the appropriate annual values from Table HE029. As a sensitivity analysis, we use a weighted average of all 3 categories – weighted according to the proportions reported by Petrou et al. (117/57/22 mild/moderate/severe) – for both outcomes.

Following NICE's guideline on asthma (NG80), we use a weighted average of costs across different levels of control and frequency of exacerbations (Price et al. 2013) to estimate an annual cost for asthma. When inflated to 2018/19 values, this amounts to £330.50 per year. As for our quality of life estimate (see I.3.5.3), we adjust this value to reflect the proportion of

people who would experience asthma even without BPD: this means we estimate a year of asthma secondary to BPD costs £294.81 over and above asthma costs for an average member of the population.

I.3.6.8 Consequences of caesarean sections for future pregnancies

Miscarriage

Our approach to estimating the costs of miscarriage is substantially based on the methods used by the National Guideline Alliance (NGA) in work commissioned by the Human Fertilisation and Embryology Authority and others (2018). We calculate the average cost of a miscarriage requiring hospital care (Table HE030) and apply that to the proportion of events that receive that level of care. Here, we diverge from the NGA's estimate. They assume only 20% of miscarriages fall into this category, based on a suggestion that there are up to 250,000 miscarriages per year in the UK, compared with around 50,000 episodes in the NHS Reference Costs. We agree that a little under 50,000 episodes is a reasonable numerator (see Table HE030); however, we believe that, for our purposes, 250,000 is an overestimate of the total number of events we should account for. This is partially because it relates to the whole of the UK (whereas NHS reference costs cover England alone). Moreover, while we do not doubt that it may be an accurate estimate of the total number of miscarriages per year including those that do not come to the attention of medical services or even the woman herself, we need to estimate those incurring medical costs. Evidence used elsewhere in our analysis suggests that 12.8% of pregnancies result in miscarriage that is recorded in medical records (Magnus et al., 2019; see I.3.3.2). Applying this proportion to the number of live births in England (603,766 in 2018/19) suggests that we would expect around 90,000 medically recorded miscarriages. Therefore, to avoid the appearance of spurious precision, we make the simple assumption that half of miscarriages coming to medical attention require hospital care. We then adopt the NGA's assumption that all miscarriages require an average of 1 GP appointment (costed at £39.23 each, per the Unit Costs of Health and Social Care, 2019). This gives us a final estimate of £666.47 × 0.5 + £39.23 = £372.47 per simulated event.

Ectopic pregnancy

The developers of NICE's guidance on ectopic pregnancy and miscarriage (NG126) undertook detailed costing for 3 ways of managing ectopic pregnancies: salpingectomy, salpingotomy and medical management. They estimated average costs of £1,608, £2,205 and £1,432, respectively. We then required an estimate of the relative frequency of each, in order to arrive at a weighted average for the typical ectopic pregnancy. However, we were unable to find any suitable data in the literature or in publicly available routine data. Therefore, we obtained a dedicated extract of Hospital Episode Statistics (HES), detailing all episodes under ICD-10 code O00. This showed that a substantial majority of activity was recorded under 11 codes: 5 indicate that salpingectomy was the major procedure in the episode (Q231, Q233, Q234, Q242, Q259; 6,880 episodes); 1 relates to salpingotomy (Q304; 71 episodes); and 3 show that no invasive procedure was carried out, suggesting medical management only (No procedure, Q555, X373; 2,449 episodes). The remaining 2 codes (Q111, Q311) relate to aspiration of products of conception, for which we have no cost estimate; however, this represents a small volume of cases (<300 total episodes), so we exclude them from calculations. We are left with a 0.732 : 0.008 : 0.261 weighting for salpingectomy, salpingotomy and medical management; applying this gives us a mean cost of £1,566.66 which, when inflated to 2018/19 value, amounts to £1,776.68. This is the cost we apply for all additional ectopic pregnancies arising in future pregnancies.

Table HE030: Unit costs for miscarriages requiring hospital treatment

Categories and codes	Submissions	Episodes	Mean (SE[a])
Nonelective			
MB08A	203	1,025	£2,034.51 (£55.34)
MB08B	363	3,495	£1,641.42 (£25.77)
Nonelective excess bed-days			
MB08A	27	274	£427.27 (£11.37)
MB08B	208	1,480	£607.04 (£13.87)
Nonelective total			
MB08A			£2,148.72
MB08B			£1,898.48
Elective			
MB08A	29	38	£2,082.31 (£262.98)
MB08B	114	882	£1,011.10 (£70.68)
Elective excess bed-days			
MB08A	3	8	£279.47 (£0.00[b])
MB08B	9	41	£157.45 (£19.21)
Elective total			
MB08A			£2,141.15
MB08B			£1,018.42
Nonelective short-stay			
MB08A	156	317	£859.99 (£28.43)
MB08B	648	39,204	£497.77 (£8.64)
Day case			
MB08A	5	7	£584.16 (£248.72)
MB08B	146	2,363	£383.85 (£21.43)
Regular admission			
MB08B	8	66	£91.01 (£0.00)
Overall total			
MB08A		1,387	£1,846.08
MB08B		46,010	£607.72
Weighted average		47,397	£643.95
Inflated from 2016/17 to 2018/19			£666.47

MB08A Threatened or Spontaneous Miscarriage, with Interventions
MB08B Threatened or Spontaneous Miscarriage, without Interventions

(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) SE unavailable because IQR=0 owing to low volume of activity

Stillbirth

Following NICE's guideline on Intrapartum care for women with existing medical conditions or obstetric complications and their babies (NG121), we obtain our estimate of the costs of stillbirth from a dedicated costing study (Campbell et al. 2017). This suggests that an average stillbirth is associated with healthcare costs of £4,191.00; when inflated to 2018/19 value, this becomes £4,527.47.

I.4 Results

I.4.1 Base-case deterministic results

I.4.1.1 Clinical outcomes

The figures below illustrate the clinical outcomes predicted by the model (that is, the outputs of each decision-tree shown in Figure HE001). Figure HE005 shows outcomes relating to infections and their consequences. Because immediate delivery is associated with fewer cases of GBS disease than expectant management (see I.3.4.1), it has lower rates of sepsis and meningitis, and consequent morbidity and mortality are proportionally lower.

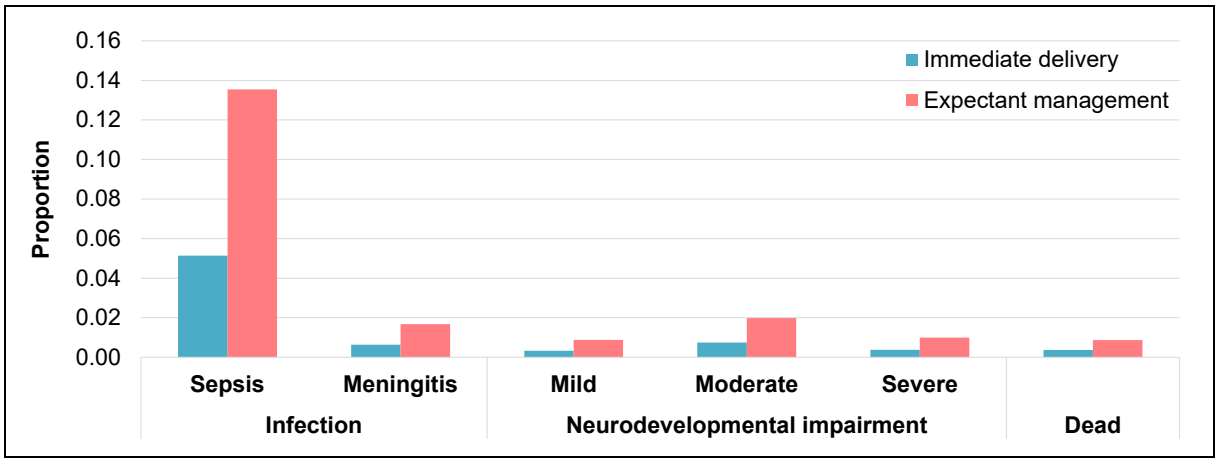


Figure HE005: Model outputs: infections and their consequences

Figure HE006 shows outcomes relating to preterm birth and its consequences (for which we use RDS as a proxy). In this case, immediate delivery is associated with higher incidence of short-term complications (see I.3.4.3) and their sequelae. Because we have retained the same vertical scale in Figure HE005 and Figure HE006, it is clear that there are more infections than cases of RDS, and many more than cases of BPD (which is the subgroup of RDS cases we assume are at risk of long-term consequences). Note that the long-term sequelae shown here refer to events over and above those that would be expected in an average newborn. For example, the prevalence of asthma in the general population is higher than indicated here, but this is our estimate of the additional cases that would arise in this population.

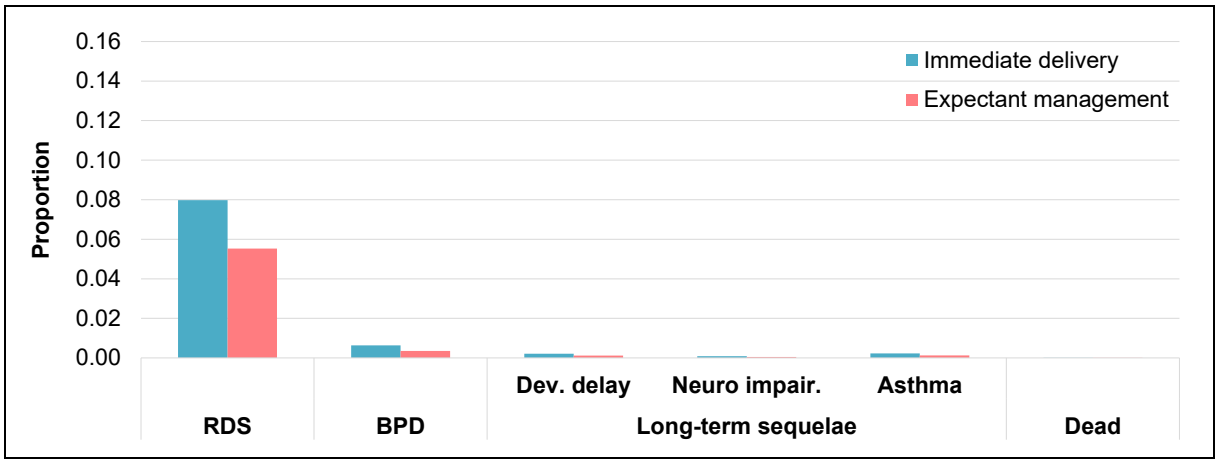


Figure HE006: Model outputs: RDS and its consequences

As shown in Figure HE007, there are more caesarean sections and fewer vaginal births with immediate delivery compared with expectant management (see I.3.4.2). The consequent effects on future pregnancies are only easily visible when it comes to the mode of delivery (again, there will be more caesarean sections in women who underwent immediate delivery for the index birth). The incidence of adverse outcomes of future pregnancies (miscarriage, ectopic, stillbirth) are all higher in the immediate delivery arm, too; however, because the effect of caesarean history on these outcomes is small (see I.3.3.2), it is hard to discern the difference in this graph.

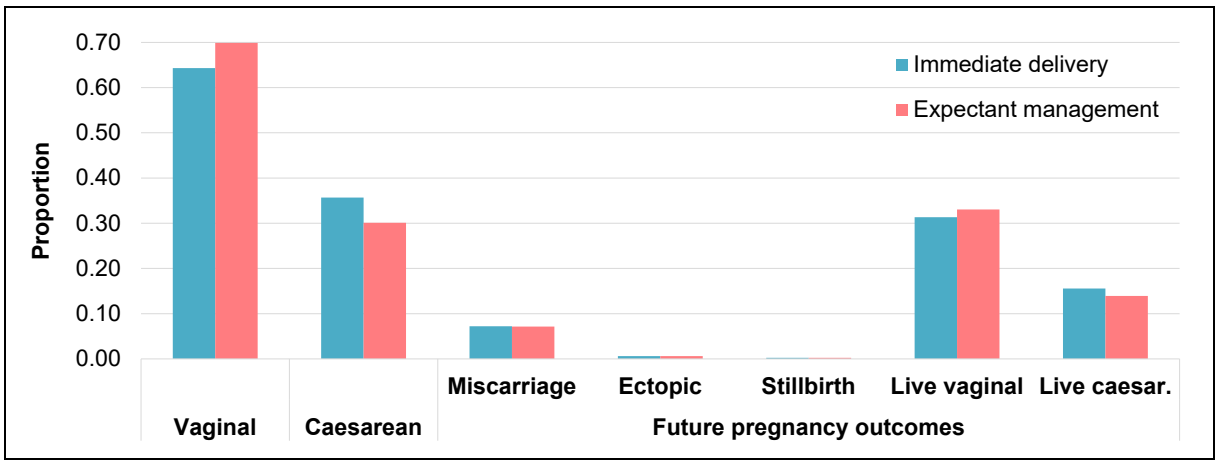


Figure HE007: Model outputs: mode of delivery and its consequences

Figure HE008 summarises all the above on a comparative scale, showing differences in expected events between the 2 approaches. The higher incidence of sepsis and infections with expectant management is clear, as is the reduction in RDS and caesarean sections. The proportion of deaths and morbidity associated with infection (favouring immediate delivery) is clearly greater than the incidence of death and morbidity following RDS (favouring expectant management).

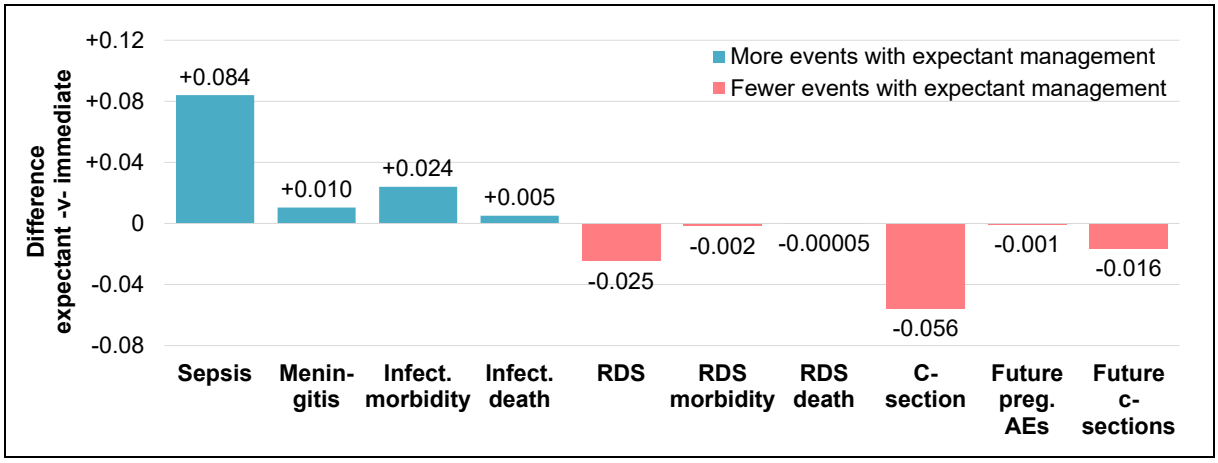
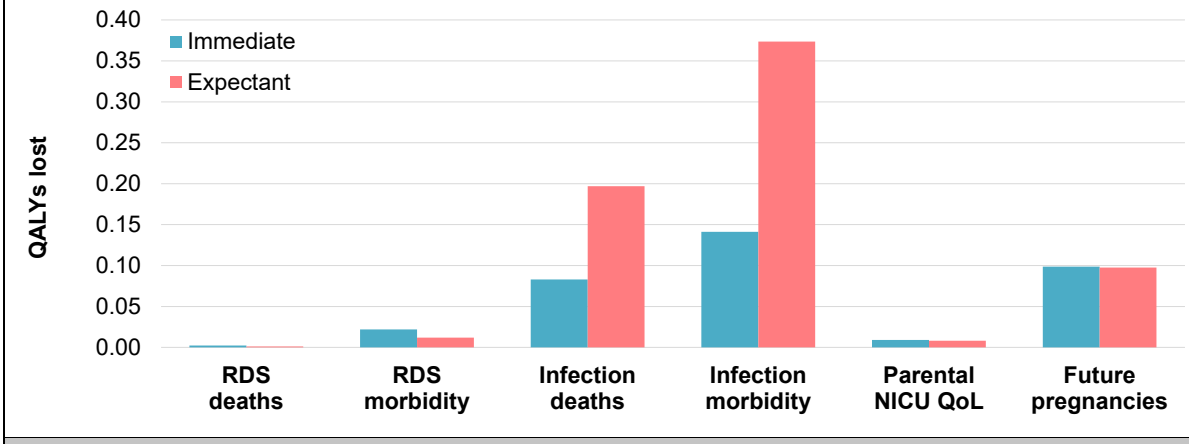


Figure HE008: Model outputs: summary of differences in events and consequences

I.4.1.2 QALYs

Figure HE009 and Figure HE010 show what happens when we translate these events into expected QALYs, on absolute and comparative scales, respectively. By far the biggest difference between strategies comes from the consequences of GBS disease: morbidity and mortality following infections amount to some 0.35 additional QALYs lost with expectant management compared with immediate delivery, whereas RDS only leads to just over 0.01 QALYs' difference between the strategies.



Lifetime QALYs lost for an average baby in our decision problem compared with an average baby without PPROM and GBS detection

Figure HE009: Modelled QALYs lost with each strategy

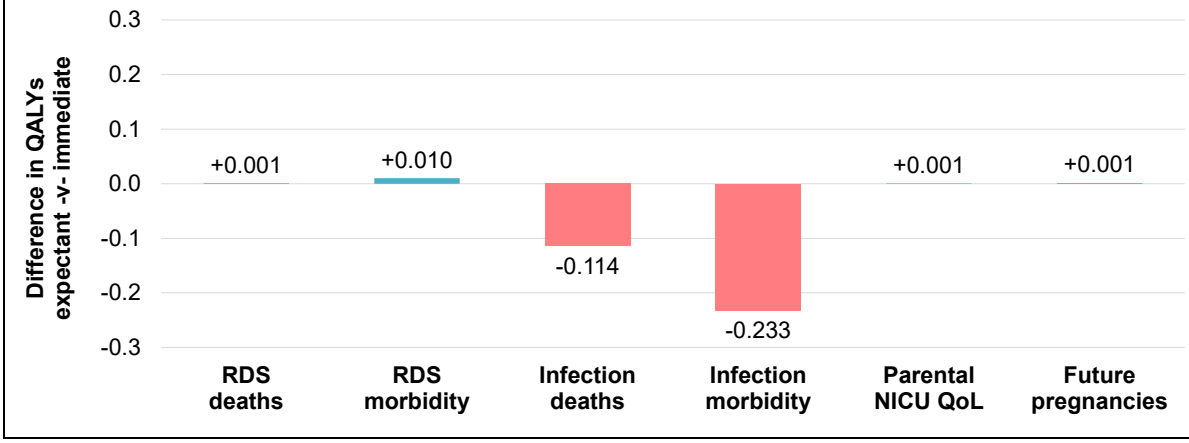


Figure HE010: Difference in modelled QALYs between the 2 strategies

I.4.1.3 Costs

As illustrated in Figure HE011 and Figure HE012, the preponderance of infection events in the expected management arm also leads to a substantial excess of costs (especially in the domain of morbidity costs: almost £4,000 per average case). In most other areas, differences between the approaches are small, with 1 exception: antenatal care is more expensive with the expectant management strategy, which is a predictable finding. The estimated difference in neonatal costs is smaller than that observed in the economic analysis of the full PPROMT population, which shows a fairly large benefit for expectant management (Lain et al., 2017). This is because the rate of infections simulated in our decision population more clearly favours immediate delivery, which attenuates any benefit for expectant management resulting from a reduced need for critical care for more premature babies.

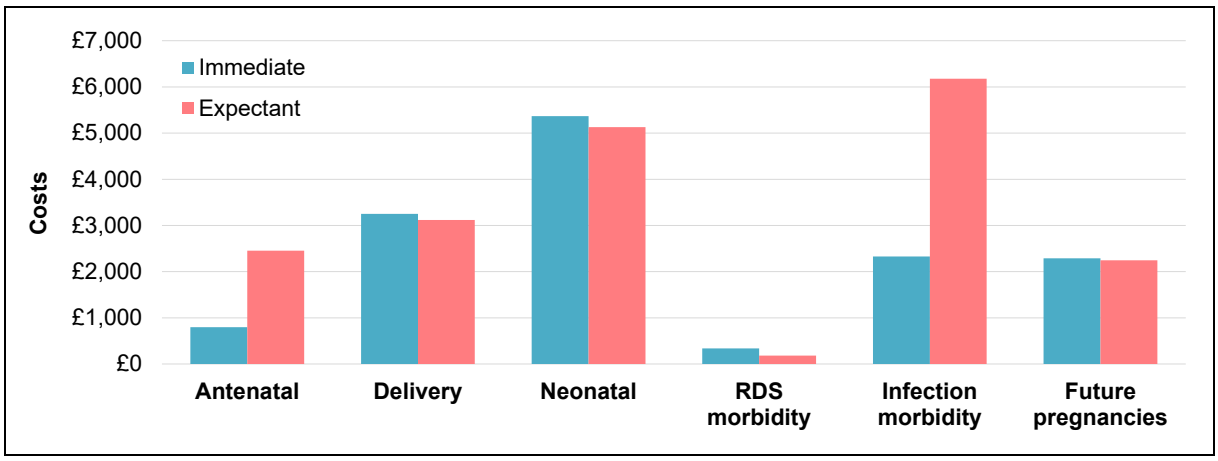


Figure HE011: Modelled costs with each strategy

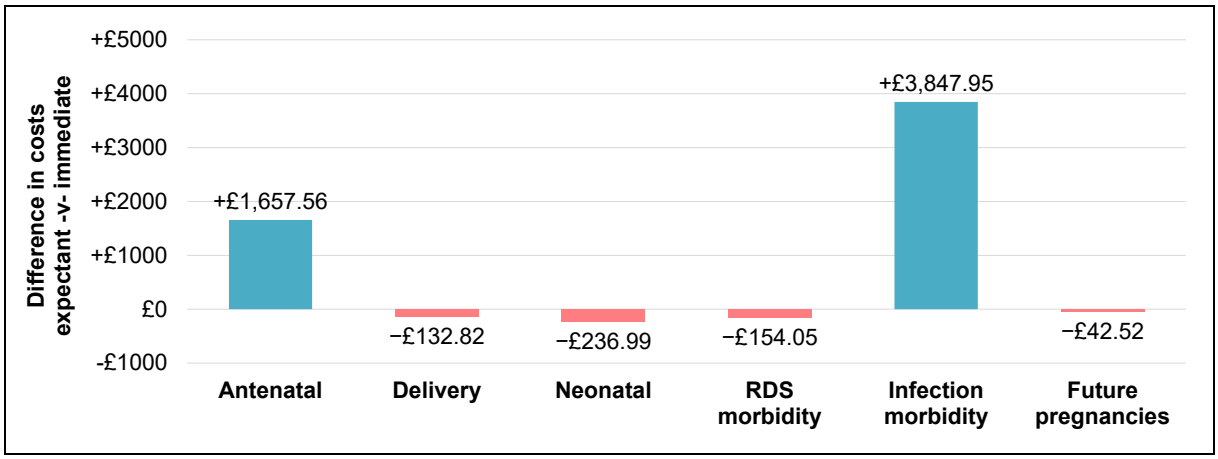


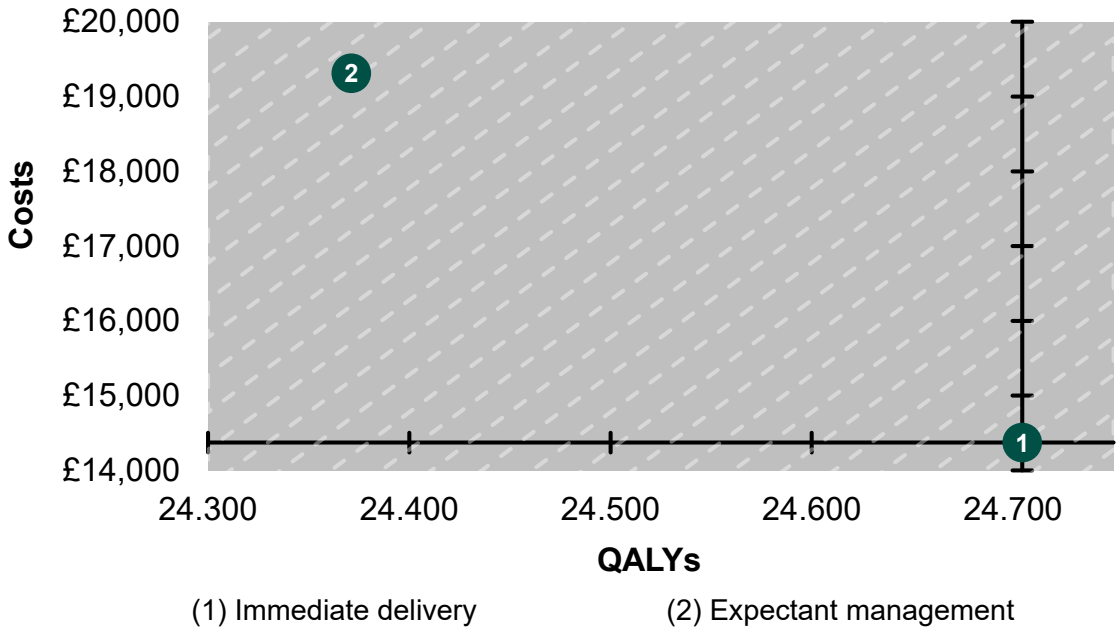
Figure HE012: Difference in modelled costs between the 2 strategies

I.4.1.4 Cost–utility

Table HE031 shows base-case deterministic results. As broken down above, immediate delivery is associated with both more QALYs than expectant management and also lower costs. Therefore, it is the dominant option. Figure HE013 plots these results on the cost–utility plane.

Table HE031: Base-case deterministic cost–utility results

Name	Absolute		Incremental			Net health benefit	
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/ QALY	£30K/ QALY
Immediate delivery	£14,372	24.705				23.986	24.226
Expectant management	£19,311	24.371	£4,939	-0.333	dominated	23.406	23.728



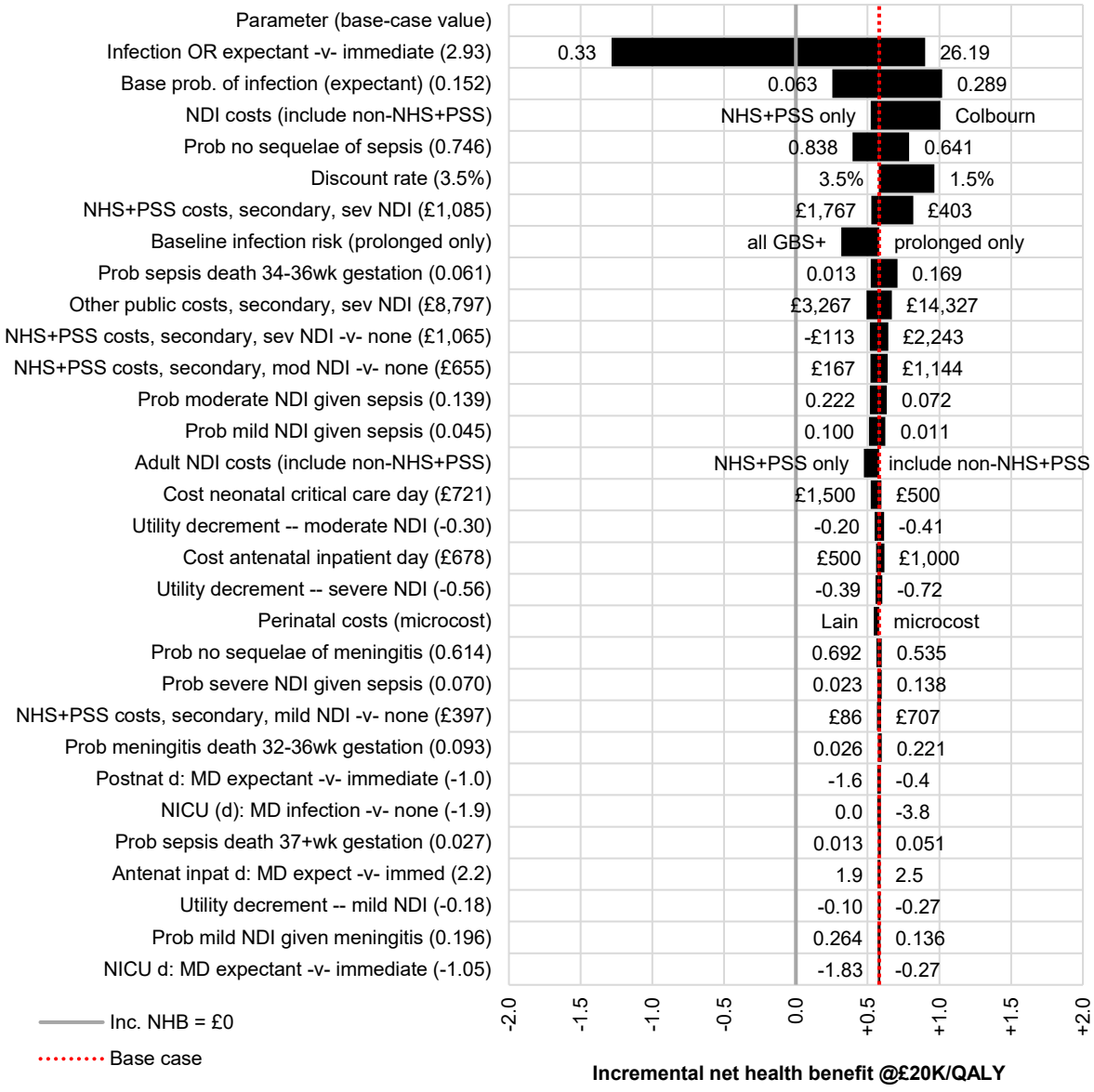
Dashed lines in background show a gradient equating to £20,000 / QALY ('iso-net benefit'). Anything below one of these lines represents better value for money than anything above it, when QALYs are valued at £20,000 each.

Figure HE013: Base-case deterministic cost–utility results

I.4.2 Sensitivity analysis

I.4.2.1 One-way sensitivity analysis

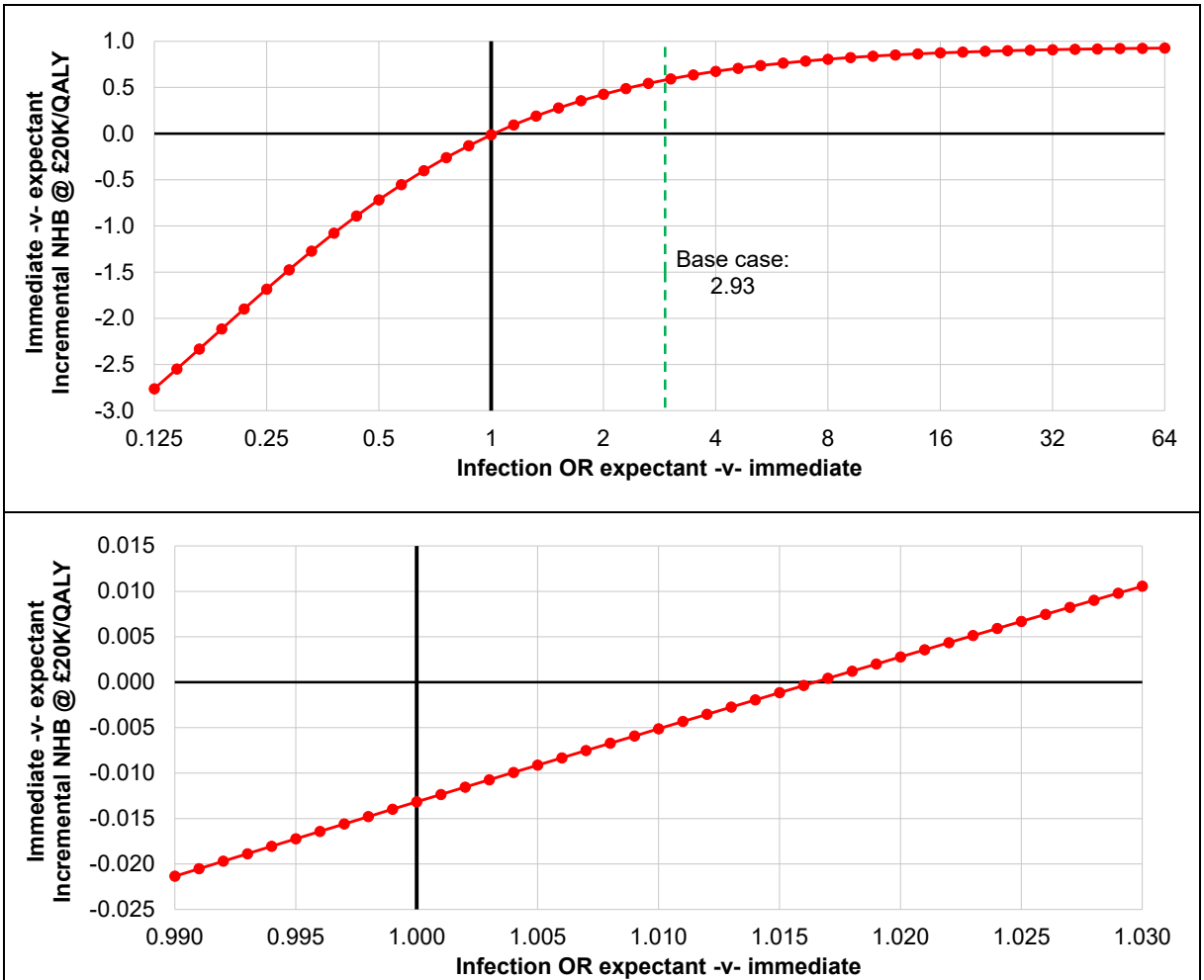
As shown in Figure HE014, when we vary each individual model input across a range plausible of values (usually, the parameter's 95% confidence limits), all-bar-1 of the parameters has no potential to overturn the superiority of immediate delivery over expectant management in our base-case results. The 1 exception is the odds ratio estimating the relative effect of strategy on the incidence of infections. At the lower bound of the 95% confidence level, the data for this parameter are consistent with expectant management resulting in fewer infection (that is, the lower end of the odds ratio is < 1; see I.3.4.1). If this were the true value of the parameter, the model would favour expectant management, as all outcomes (infections, RDS, delivery) would favour that approach over immediate delivery.



30 most influential parameters shown. Positive incremental net health benefit implies immediate delivery is the preferred option (i.e. it would be associated with an ICER of £20,000/QALY or better compared with expectant management)

Figure HE014: One-way sensitivity analysis – tornado diagram

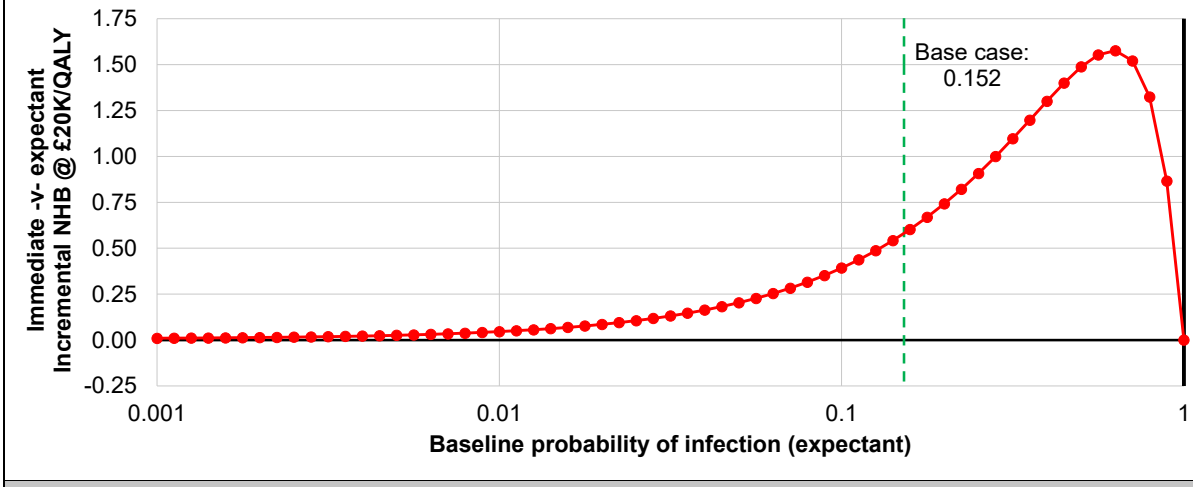
As the odds ratio for infections is clearly the critical parameter in determining the outputs of the model, we performed more detailed one-way analysis to explore its influence. The top panel of Figure HE015 appears to show that value for money is a direct function of this parameter: when it takes a value of less than 1, the model favours expectant management; when it rises above this level, immediate management becomes the preferred option. When we zoom in to the origin of the graph (the lower panel), we can see that the precise point at which incremental net benefit becomes positive (in immediate delivery's favour) is when the odds ratio rises above 1.015. The line does not cross at exactly OR=1 because of the other negative consequences with which immediate delivery is associated (higher rates of RDS and caesarean sections). However, this analysis shows that the odds of infection only have to be more than 1.5% higher with expectant management for the benefit of avoiding them to outweigh the other disadvantages of immediate delivery.



Positive incremental net health benefit – when the red line is above the horizontal axis – implies immediate delivery is the preferred option (i.e. it would be associated with an ICER of £20,000/QALY or better compared with expectant management)

Figure HE015: One-way sensitivity analysis – odds ratio for infection

We also performed a detailed one-way sensitivity analysis on the baseline probability of infection (to which the model applies the odds ratio discussed above; see I.3.3.1). This suggests that, at very low infection probabilities, the net benefit with which immediate delivery is associated is attenuated; however, it remains positive unless infections are either impossible or inevitable.



Positive incremental net health benefit implies immediate delivery is the preferred option (i.e. it would be associated with an ICER of £20,000/QALY or better compared with expectant management)

Figure HE016: One-way sensitivity analysis – baseline probability of infection

I.4.2.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (Figure HE017) shows an obvious degree of correlation between costs and QALYs. This is, once more, a result of the predominance of the odds ratio for infection in determining model outputs: when a high OR is sampled, immediate delivery is associated with both lower costs and higher QALYs; when a low OR is sampled, that relationship is reversed. The mean of the probabilistic outputs is somewhat closer to the origin of the cost–utility plane than the deterministic result (expected incremental costs fall from almost £5,000 to £3,556 and expected incremental QALYs fall from −0.333 to −0.219). This occurs because, in the deterministic calculations, the critical odds ratio is evaluated at its conventional point estimate, which reflects the modal value, not the mean, of the expected distribution (see Briggs et al. 2006, p. 90).

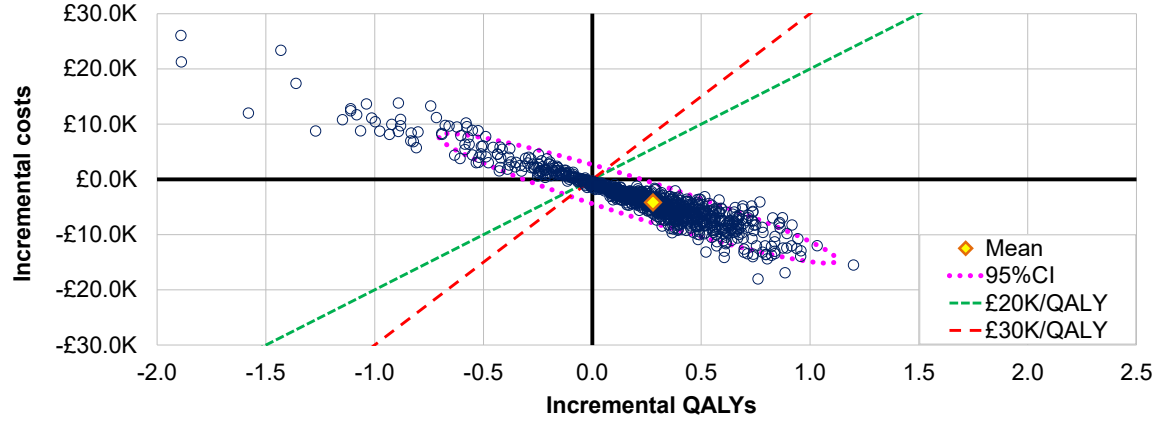
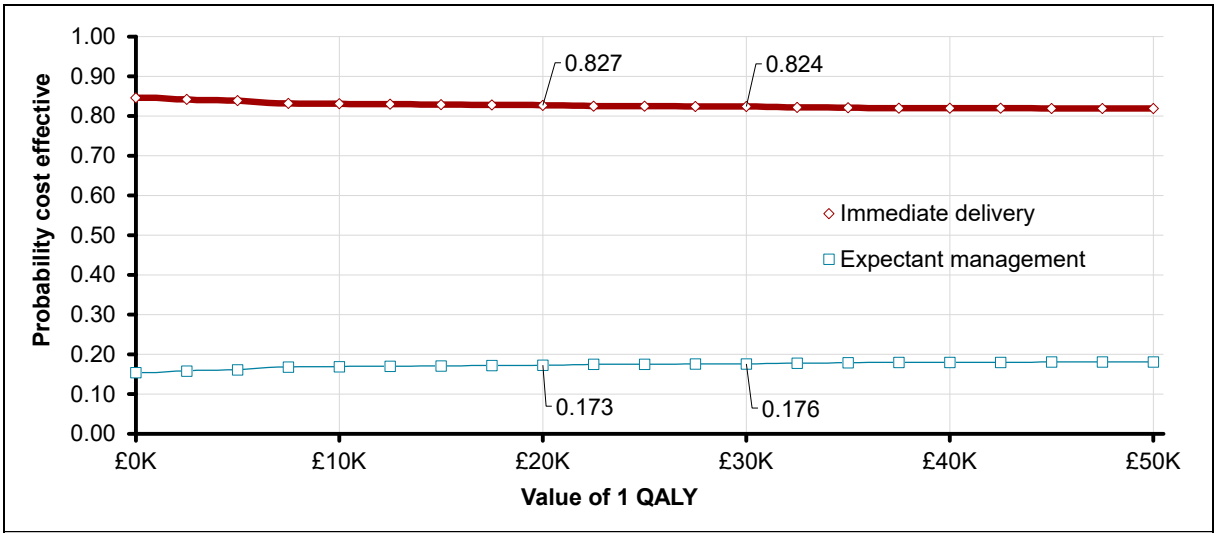


Figure HE017: Probabilistic sensitivity analysis – cost–utility scatterplot

The cost-effectiveness acceptability curve (CEAC; Figure HE018) is characteristic of an economic analysis with substantial correlation between costs and QALYs. The optimal option is almost entirely invariant to the value that we place on QALYs; this is because, in any given simulation, the model predicts either that immediate delivery dominates expectant management, or that expectant management dominates immediate delivery. As a result, the value we place on QALYs is essentially immaterial. Because the probability mass in the

distribution for the infection odds ratio quite strongly favours immediate delivery, a little over 80% of simulations suggest that is the preferred option.



Bold line shows cost-effectiveness acceptability frontier (CEAF)

Figure HE018: Probabilistic sensitivity analysis – cost-effectiveness acceptability curve

I.5 Discussion

I.5.1 Principal findings

The base-case model finds that immediate delivery dominates expectant management to a relatively substantial degree – that is, it is associated with both meaningfully higher QALYs and meaningfully lower costs. Sensitivity analysis shows that the odds ratio estimating the relative likelihood of infection between the 2 approaches is by far the greatest contributor to model uncertainty. At a 95% confidence level, the RCT data are consistent with immediate delivery having a higher rate of infections and, if this were the case, expectant management would be the preferred option.

These results arise because our model predicts that the lifetime discounted costs and consequences associated with a neonatal GBS infection far outweigh those that can be expected from the complications of late-preterm birth (for which we use RDS as a proxy). The model estimates that an average case of neonatal GBS infection is associated with discounted lifetime costs of approximately £40,000 and discounted lifetime effects of about 3.8 QALYs lost (undiscounted figures are c£130,000 and c11.0 QALYs lost). This implies that society should be prepared to pay over £115,000 per case of GBS prevented.

I.5.2 Strengths

This is the first economic analysis of this decision problem (focusing on GBS+ mothers with PPROM in particular), and the first of any type of late-preterm PPROM to estimate QALYs, accounting for lifelong morbidity and mortality associated with infection and other outcomes. 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.

I.5.3 Limitations

A perfect model of this problem would use evidence directly reporting lifelong effects of the decision. Of course, no such data exist. Therefore, our challenge was to move from the short-term outcomes reported in the RCTs to QALYs over a lifetime. Estimating the impact of neonatal infections using observational evidence describing the mortality and long-term morbidity with which such events are associated is an established approach (see e.g. Colbourn et al. 2007, CG149, Giorgakoudi et al. 2018, Grosso et al. 2019). Our methods for estimating the long-term consequences of late-preterm delivery are more innovative. We use incidence of RDS as a proxy measure, which enables us to tie long-term outcomes to an outcome observed in the RCTs. To do this, we use evidence on chronic lung disease (BPD) and its consequences. However, this comes from cohorts that, while they do not exclude late-preterm babies, will predominantly represent more premature infants. Indeed, the committee advised that, in the UK, BPD is seldom used as a diagnosis in late-preterm babies (though noted that such neonates sometimes require prolonged oxygen support, which is the primary diagnostic criterion in most definitions of BPD). We adjusted for gestational age when assessing this outcome, so that our estimates are as representative as possible of the population of interest. We note that a large RCT in babies born at 34^{+0}–36^{+6} weeks' gestation found an BPD incidence rate of 0.6% in its control arm (Gyamfi-Bannerman et al. 2016); this is identical to the rate we predict for the immediate delivery arm of our model (see I.4.1.1). Therefore, while it relies on some evidence from outside our late-preterm population, we are confident that our approach appropriately enables us to take advantage of a short-term outcome that is reported in relevant RCTs in order to estimate lifelong impacts.

As described in I.3.5.1, 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 the event, being able to capture this impact would have minimal effect on our model. This is because uncertainty in model outputs overwhelmingly results from imprecision in the likelihood of infection, not in the impact of any events that transpire (in other words, additional information about the full impact of infections would widen the spread of outputs, but they would still centre around the same point of equilibrium).

I.5.4 Comparison with other published economic analyses

Our systematic review of published economic analyses identified 1 study that is of indirect relevance to this question (Lain et al. 2017; see 1.1.7, above). We used evidence from this study, where appropriate, to underpin cost inputs to our model (see I.3.6.1). As a result, our short-term cost estimates correspond fairly closely with theirs. Lain et al. do not estimate long-term costs or effects; however, at their point estimates, their results suggest that immediate delivery costs around £16,000 per infection prevented. As noted in I.5.1, above, our calculations suggest that the cost and QALY impacts of infections are far greater than this figure, which means that immediate delivery can be considered excellent value for money, compared with expectant management.

I.6 Critical appraisal of original model

Table HE032: 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	Empirical data on problems of prematurity would enhance model; using RDS and its sequelae as proxy is a reasonable alternative
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	Data on mortality do not distinguish between sepsis and meningitis at different gestational ages
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?	Yes	
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	
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**	

1 Appendix J – Excluded studies

2 Clinical studies

Study	Reason for exclusion
Abenhaim, HA and Fraser, WD (2007) Review: planned early birth after prelabour rupture of membranes at term has benefits for mother and infant: commentary. Evidence-based medicine 12(1): 16	- Article commentary
Bond, DM, Middleton, P, Levett, KM et al. (2017) Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. Cochrane Database of Systematic Reviews	- More recent systematic review included that covers the same topic
Bouchghoul, H. (2020) Term Prelabor Rupture of Membranes: CNGOF Guidelines for Clinical Practice - Initial Management. Gynecologie Obstetrique Fertilite et Senologie 48(1): 24-34	- Study not reported in English
C, AB (2016) Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPROMT trial): a randomised controlled trial: editorial comment. Obstetrical & gynecological survey 71(4): 207-209	- Article commentary
Milasinovic, L, Radeka, G, Petrovic, D et al. (1998) Premature rupture of the fetal membranes--an active or expectant approach in management of this obstetrical problem. Medicinski pregled 51(78): 346-349	- Study not reported in English
Bond D.M., Middleton P., Levett K.M. et al. (2017) Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. Cochrane Database of Systematic Reviews 2017(3): cd004735	- Systematic review that does not contain population of interest [Women with PPROM but not GBS detected]
Buchanan S.L., Crowther C.A., Levett K.M. et al. (2010) Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. Cochrane database of systematic reviews (Online) 3: cd004735	- More recent systematic review included that covers the same topic
Buchanan Sarah L, Crowther Caroline A, Levett Kate M, Middleton Philippa, Morris Jonathan (2010) Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. Cochrane Database of Systematic Reviews: Reviews issue3	- More recent systematic review included that covers the same topic
Delorme P. and Garabedian C. (2018) Modalities of birth in case of uncomplicated preterm premature rupture of membranes: CNGOF Preterm Premature Rupture of Membranes Guidelines. Gynecologie Obstetrique Fertilite et Senologie 46(12): 1068-1075	- Study not reported in English
Grobman, William A and Caughey, Aaron B (2019) Elective induction of labor at 39 weeks compared with expectant management: a meta-analysis of cohort studies. American journal of obstetrics and gynecology 221(4): 304-310	- Not a relevant study design *Meta-analysis of cohort studies*
Hartling, Lisa, Chari, Radha, Friesen, Carol et al. (2006) A systematic review of intentional delivery in women with preterm prelabor rupture of membranes.. 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 19(3): 177-87	- Sysytematic review checked for additional includes

Study	Reason for exclusion
Hobbins, JC (2016) Preterm Premature Rupture of Membranes: when to Deliver?. OB/GYN clinical alert 33(4): 25-26	- Not a relevant study design *Article commentary*
Iane A.-M.; Chicireanu M.; Peltecu G. (2009) Preterm premature rupture of membranes. Gineco.ro 5(2): 80-83	- Review article but not a systematic review
Lain S.J., Roberts C.L., Bond D.M. et al. (2017) An economic evaluation of planned immediate versus delayed birth for preterm prelabour rupture of membranes: findings from the PPROMT randomised controlled trial. BJOG: An International Journal of Obstetrics and Gynaecology 124(4): 623-630	- Economic analysis of incuded study
Mercer, B M, Crocker, L G, Boe, N M et al. (1993) Induction versus expectant management in premature rupture of the membranes with mature amniotic fluid at 32 to 36 weeks: a randomized trial.. American journal of obstetrics and gynecology 169(4): 775-82	- Study does not contain population of interest [Results not separated by group B streptococcus colonisation]
Naef, R W 3rd, Allbert, J R, Ross, E L et al. (1998) Premature rupture of membranes at 34 to 37 weeks' gestation: aggressive versus conservative management.. American journal of obstetrics and gynecology 178(1pt1): 126-30	- GBS colonisation not an inclusion critria
Nelson, L H, Meis, P J, Hatjis, C G et al. (1985) Premature rupture of membranes: a prospective, randomized evaluation of steroids, latent phase, and expectant management.. Obstetrics and gynecology 66(1): 55-8	- Study does not contain population of interest [Women between 28 to 34 weeks gestation]
Ohlsson, A (1989) Treatments of preterm premature rupture of the membranes: a meta-analysis.. American journal of obstetrics and gynecology 160(4): 890-906	- Systematic review that does not contain population of interest
Quist-Nelson, Johanna, de Ruigh, Annemijn A, Seidler, Anna Lene et al. (2018) Immediate Delivery Compared With Expectant Management in Late Preterm Prelabor Rupture of Membranes: An Individual Participant Data Meta-analysis.. Obstetrics and gynecology 131(2): 269-279	- Sysytematic review checked for additional includes
van der Ham, David P, Nijhuis, Jan G, Mol, Ben Willem J et al. (2007) Induction of labour versus expectant management in women with preterm prelabour rupture of membranes between 34 and 37 weeks (the PPROMEXIL-trial).. BMC pregnancy and childbirth 7: 11	- GBS colonisation not an inclusion critria [Women included irrespective of GBS status]
van der Ham, David P, van der Heyden, Jantien L, Opmeer, Brent C et al. (2012) Management of late-preterm premature rupture of membranes: the PPROMEXIL-2 trial.. American journal of obstetrics and gynecology 207(4): 276e1-10	- Systematic review that does not contain population of interest [GBS status not specified]
van der Ham, David P, Vijgen, Sylvia M C, Nijhuis, Jan G et al. (2012) Induction of labor versus expectant management in women with preterm prelabor rupture of membranes between 34 and 37 weeks: a randomized controlled trial.. PLoS medicine 9(4): e1001208	- GBS colonisation not an inclusion critria [Not an exclusion criteria but results not separated by GBS status]
Van Der Heyden J.L., Willekes C., Van Baar A.L. et al. (2015) Behavioural and neurodevelopmental outcome of 2-year-old children after preterm premature rupture of membranes: Follow-up of a randomised clinical trial comparing induction of labour and expectant	- Study does not contain population of interest [Results not separated by GBS colonisation]

Study	Reason for exclusion
management. European Journal of Obstetrics and Gynecology and Reproductive Biology 194: 17-23	
Vijgen, Sylvia M C, van der Ham, David P, Bijlenga, Denise et al. (2014) Economic analysis comparing induction of labor and expectant management in women with preterm prelabor rupture of membranes between 34 and 37 weeks (PPROMEXIL trial).. Acta obstetricia et gynecologica Scandinavica 93(4): 374-81	- Economic analysis of incuded study

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2 **Economic studies**

Study	Reason for exclusion
Marshall VA. Management of premature rupture of membranes at or near term. Journal of nurse-midwifery. 1993 May 1;38(3):140-5.	Different population; the study is addressing women at term.
Gafni A, Goeree R, Myhr TL, Hannah ME, Blackhouse G, Willan AR, Weston JA, Wang EE, Hodnett ED, Hewson SA, Farine D. Induction of labour versus expectant management for prelabour rupture of the membranes at term: an economic evaluation. Cmaj. 1997 Dec 1;157(11):1519-25.	Different population; the study is addressing women at term.
Yasmin S, Yasmin A, Khattak NN, Karim R, Raees M. ACTIVE VERSUS CONSERVATIVE MANAGEMENT OF PRELABOUR RUPTURE OF MEMBRANES AT TERM. Journal of Postgraduate Medical Institute (Peshawar-Pakistan). 2012 Dec 14;27(1).	Different population; the study is addressing women at term.
Vijgen, S.M., Van der Ham, D.P., Bijlenga, D., Van Beek, J.J., Bloemenkamp, K.W., Kwee, A., Groenewout, M., Kars, M.M., Kuppens, S., Mantel, G. and Molkenboer, J.F., 2014. Economic analysis comparing induction of labor and expectant management in women with preterm prelabor rupture of membranes between 34 and 37 weeks (PPROMEXIL trial). Acta obstetricia et gynecologica Scandinavica, 93(4), pp.374-381.	Not a full cost-utility analysis and not a UK study.
van der Ham DP, Nijhuis JG, Mol BW, van Beek JJ, Opmeer BC, Bijlenga D, Groenewout M, Arabin B, Bloemenkamp KW, van Wijngaarden WJ, Wouters MG. Induction of labour versus expectant management in women with preterm prelabour rupture of membranes between 34 and 37 weeks (the PPROMEXIL-trial). BMC pregnancy and childbirth. 2007 Dec;7(1):11.	Not a full cost-utility analysis and not a UK study.
Caughey AB. The importance of economic analyses in health care: examining the economics of preterm prelabour rupture of membranes care. BJOG: An International Journal of Obstetrics & Gynaecology. 2017 Mar;124(4):551-2.	Not an economic evaluation study
American College of Obstetricians and Gynecologists. Practice Bulletin No. 171: Management of Preterm Labor. Obstetrics and gynecology. 2016 Oct;128(4):e155.	Not an economic evaluation study and not a UK study
Morris JM, Roberts CL, Crowther CA, Buchanan SL, Henderson-Smart DJ, Salkeld G. Protocol for the immediate delivery versus expectant care of women with preterm prelabour rupture of the membranes close to term (PPROMT) Trial [ISRCTN44485060]. BMC pregnancy and childbirth. 2006 Dec;6(1):9.	A study protocol

Study	Reason for exclusion
Grable IA. Cost-effectiveness of induction after preterm premature rupture of the membranes. American journal of obstetrics and gynecology. 2002 Nov 1;187(5):1153-8.	Not a full cost-utility analysis and not a UK study.

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Appendix K – Research recommendations – full details

K.1 Research recommendation

What is the impact of neonatal infection on the health-related quality of life of the baby's family and carers?

K.2 Why this is important

Two RCTs were identified which compared the effects of immediate delivery and expectant management for women with PPROM at a gestational age between 34+0 and 37+6 weeks. While these studies reported on outcomes for the baby, there was limited information for outcomes in the mother and no information on outcomes for the wider family. While neonatal infection can have serious consequences for the baby, there is also the potential for a considerable impact on the family.

Research is needed using a robust study design such as prospective cohort studies which examine both the short-term and long-term impact on the family of a baby who develops neonatal infection. Research in this area is essential to understand the wider impact of neonatal infection, beyond the direct effects that are experienced by the baby.

K.3 Rationale for research recommendation

Importance to 'patients' or the population	Neonatal infection can have serious consequences for the health of a baby, but also negative consequences for family members of the baby. Currently, little is known about the short-term and long-term effects of neonatal infection on the baby's parents, carers and siblings. By understanding the impact of neonatal infection on the baby's family, it will be possible to provide information and support to families when their baby is diagnosed and treated for infection. This may help to improve both short-term and long-term outcomes for the family.
Relevance to NICE guidance	The economic modelling undertaken for this question was somewhat hampered by being unable to estimate the impact of infection on families and carers, which is likely to be an important component of the full impact of decision-making, in this area. The committee have made recommendations on information and support that should be given to the baby's family. However, there was limited evidence and so much of this was based on clinical experience. Future research will help to provide more specific guidance on what information and support should be given to families, both at the time of the baby's diagnosis and longer term.
Relevance to the NHS	The outcome would help to understand the wider impact of neonatal infection on the baby's family. This would help clinicians to give the family the most appropriate information and support. It will also provide more detailed information for use in future health economic modelling.

National priorities	Medium
Current evidence base	This review identified 2 RCTs reporting data on women who have PPROM and are between 34+7 and 36+6 weeks' gestation. These studies reported on neonatal outcomes, but there was no information on outcomes for the family of the baby.
Equality considerations	No specific equality concerns are relevant to this research recommendation.

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K.124 Modified PICO table

PICO	**Population:** Families/carers of babies with neonatal infection or meningitis **Phenomenon of interest:** Family/carer outcomes where a baby in the family develops neonatal infection or meningitis **Outcomes:** • Quality of life (including EQ-5D) • Mental health • Postnatal depression • Anxiety in parents, carers and siblings • Post-traumatic stress disorder • Delaying subsequent pregnancies • Marital and family breakdown
Current evidence base	No current evidence
Study design	Case-control studies
Other comments	Study should be adequately powered and should collect data on both short- and long-term outcomes. Studies should use quantitative methods of data collection

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