Universal antenatal culture-based screening for maternal Group B *Streptococcus* (GBS) carriage to prevent early-onset GBS disease

External review against programme appraisal criteria for the UK National Screening Committee

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List of Abbreviations

AMSTAR	A Measurement Tool to Assess Systematic Reviews
ANOVA	Analysis of variance
BPSU	British Paediatric Surveillance Unit
CC	Clonal complex
CDC	Centers for Disease Control and Prevention
CFU	Colony forming units
CI	Confidence intervals
Co-amoxiclav	Amoxicillin-clavulanate
CODAC	Causes of Death and Associated Conditions
CSF	Cerebrospinal fluid
E. coli	*Escherichia* coli
EOGBS	Early-onset neonatal group B *Streptococcus* disease
FN	False negative
FP	False positive
GBS	Group B *Streptococcus*
HES	Hospital Episode Statistics
IAP	Intrapartum antibiotic prophylaxis
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range (25^{th} to 75^{th} percentile)
IV	Intravenous
LOGBS	Late-onset neonatal group B streptococcus disease
MBRRACE-UK	Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK
NA	Not applicable
NEC	Necrotising enterocolitis
NI	Northern Ireland
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
NISRA	Northern Ireland Statistics and Research AgencyNPV Negative predictive value
NR	Not reported
NSC	National Screening Committee
ONS	Office of national statistics
OR	Odds ratio
PCR	Polymerase chain reaction
PHE	Public Health England
PPROM	Preterm pre-labour rupture of membranes
PPV	Positive predictive value
PROM	Prolonged rupture of membranes
QALY	Quality-adjusted life year
QUIPS	Quality in Prognosis Studies
RCOG	Royal College of Obstetricians & Gynaecologists

RCT	Randomised controlled trials
REA	Rapid evidence assessment
RoB	Risk of Bias
RoBANS	Risk of Bias Assessment Tool for Nonrandomised Studies
RoI	Republic of Ireland
RR	Relative risk
ST	Sequence type
TN	True negative
TP	True positive
UK	United Kingdom
USA	United States of America

Plain English Summary

This report updates the evidence for screening pregnant women to find out if they carry the germ, or 'bacterium', Group B *Streptococcus* (GBS). This review will help to inform decisions about whether the benefits of introducing GBS screening would outweigh the harms.

Group B *Streptococcus* (GBS) is naturally carried by healthy men and women. About one in five pregnant women carry GBS in their gut, vagina or urinary tract. It does not usually cause symptoms or harm. If a woman is carrying GBS in labour, there is a small chance that it can pass to the baby. When this happens most newborn babies are not affected by GBS, but a small number of babies develop a serious condition in the first six days of life. This is called 'Early-Onset GBS infection' (EOGBS). EOGBS can cause blood poisoning, pneumonia and meningitis. Most babies with EOGBS will survive and will be healthy. Unfortunately, even with the best care, a small number die and some who recover have after effects like deafness or brain damage.

In order to prevent GBS infection in babies, during labour pregnant women can be given antibiotics (through a drip). Antibiotics are given as soon as possible once labour starts and then at regular intervals until the baby is born.

At the moment the National Health Service (NHS) offers this treatment to women who are known to carry GBS, or who have risk factors for EOGBS. Risk factors include a high temperature during labour, or a previous baby with EOGBS. Currently not all women with risk factors are having the antibiotic treatment during labour, which may be in part due to the woman's personal preference (as the drip can limit childbirth options).

Routine screening of all pregnant women has been suggested to identify pregnant women who carry GBS. This screening test would be performed at 35–37 weeks of pregnancy and involves a swab test of the vagina and rectum. The cells from the swabs are grown to see if GBS is present. All women that are found to carry GBS would be offered antibiotics through a drip in labour.

EOGBS is a serious condition and the review found that about one in every 1,750 babies born in the UK and the Republic of Ireland develops EOGBS. About one in 19 babies with EOGBS will die from the infection.

However the review does not recommend that screening should be introduced in the UK. There are number of reasons for this.

- The proposed screening programme would offer all 718,000 women pregnant at 37 weeks in the UK each year, a test for GBS colonisation in the third trimester of pregnancy
- If they all accepted the test, around 150,800 would test positive and be offered antibiotics during labour through a drip.
- Only 333 of these 150,800 women would have babies that develop EOGBS, because the test is inaccurate for predicting EOGBS infection in the baby. The rest would receive unnecessary treatment.
- We do not know whether there are any short or long-term harms to the mother or baby from giving antibiotics to the mother during labour, and so do not know how many of the 150,800 treated women and babies might be harmed.
- The purpose of a screening programme should be to prevent EOGBS disease in the baby and particularly its worst effects. From the available research we do not know whether giving antibiotics in labour to women with a positive GBS screening test reduces the number of babies dying from EOGBS.

- There was some evidence that the introduction of antenatal GBS screening for all pregnant women may lower the number of babies with EOGBS, but the review found that these studies have limitations, which means that their findings may not be true.

Because of these findings it is not possible to know whether the introduction of a screening programme in the UK would do more good than harm.

We need more research to identify which pregnant women will go on to have a baby which develops EOGBS disease.

Executive Summary

Introduction

Group B *Streptococcus* is a naturally occurring gram-positive bacterium that colonises the gastrointestinal and genitourinary tract in 20–25% of pregnant woman. When a woman carries GBS in labour, there is a 36% chance that GBS might be transmitted to her neonate. Most neonates with GBS colonisation will be asymptomatic; however, 1% will suffer from invasive GBS. When this occurs in the first six days of life it is known as Early Onset GBS (EOGBS). EOGBS is one of the most important causes of neonatal sepsis and subsequent morbidity and mortality globally. Up to 10% of those affected with EOGBS will die as a result.

The aim of this review is to update and summarise the evidence on the key questions relating to universal antenatal screening for GBS carriage, since the last UK NSC review in 2012. We investigated whether there have been any significant developments in the evidence base. These questions were on: the incidence, epidemiology, and natural history of GBS, the diagnostic accuracy of culture tests, the treatment for GBS maternal colonisation, and the clinical- and cost-effectiveness of a GBS screening programme. The key questions were:

Condition and epidemiology (UK NSC criterion 1)

1. What is the overall incidence of EOGBS in the UK?
2. What is the distribution of EOGBS by maternal risk factors in the UK?
3. What is the clinical presentation of EOGBS in the UK?
4. What is the overall mortality rate attributable to EOGBS in live born babies in the UK?
5. How is the mortality attributable to EOGBS distributed by maternal risk factors in the UK?
6. What short-term morbidities are associated with EOGBS in the UK?
7. What proportion of EOGBS cases has long-term mild or severe morbidities?
8. What is the association between EOGBS clinical presentation and morbidity outcomes?
9. What proportion of stillbirths is associated with GBS each year in the UK, and does this reliably contribute to estimates of GBS associated mortality?
10. What is the relationship between gestational age and GBS-related stillbirths in the UK?

Natural history (UK NSC criterion 1)

11. What is the maternal GBS carriage rate in the UK?
12. What proportion of antenatal screen positive and screen negative women transition in terms of carriage status at term?
13. What proportion of screen positive women at term transmits the bacterium to the baby?
14. What proportion of colonised babies is affected by EOGBS?
15. Are there bacterial loads and/or bacterial molecular markers predictive of GBS transmission (from maternal colonisation to neonatal colonisation or EOGBS disease) or GBS transition (from neonatal GBS colonisation to EOGBS disease)?

Test accuracy (UK NSC criterion 4)

16. What is the sensitivity and specificity of selective antenatal culture screening tests?

17. What is the predictive value of selective antenatal culture screening tests for a) carriage status at term and b) EOGBS disease?

Intrapartum antibiotic prophylaxis (IAP) treatment clinical effectiveness (UK NSC criterion 9)

18. What is the reported effectiveness of IAP in preventing EOGBS related morbidity and mortality in screen-detected populations?
19. What is the reported effectiveness of IAP in preventing culture negative/probable EOGBS in screen-detected populations?
20. What adverse events do women or children experience after receiving IAP treatment for any prophylactic reason?

Screening clinical effectiveness (UK NSC criterion 11)

21. What is the clinical effectiveness of GBS screening on EOGBS-related mortality and morbidity, neonatal sepsis and neonatal sepsis-related mortality?

Screening cost-effectiveness (UK NSC criterion 14)

22. What is the cost effectiveness of GBS screening in the UK?

Methods

Two different methods were used for this review. For question 15 (GBS bacterial load and molecular markers) and question 20 (adverse events from IAP), full systematic review methods were used, as these were new questions that have not been previously reviewed. For the remaining questions, a rapid review approach was used. For all reviews, Medline, Embase and The Cochrane Library were searched, as well as Web of Science for the systematic reviews. Articles were limited to the English language and humans. The rapid review was also limited to publication from 2012 onwards. Published reports from Public Health England (PHE), and the British Paediatric Surveillance Unit (BPSU) were searched for questions 1-6 and 8; unpublished data from Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries (MBRRACE-UK) were used for questions 4, 9, and 10. Experts in the field reviewed the final list of included studies and for questions 15 and 20, the reference lists of included papers and relevant reviews were checked.

Reviewers independently screened titles and abstracts of all records identified by the searches, and assessed full-texts of all articles deemed potentially relevant for inclusion. Reviewers used an electronic, piloted data extraction form. Formal quality assessment was not undertaken for key questions 1-14. For the quality appraisal of questions 16-20, standard quality assessment tools were used (Question 16-17: unadjusted QUADAS-2; Question 15: Quality in Prognostic Studies [QUIPS]; Question 18-21: Cochrane Risk of Bias [RoB] tool for randomised studies and Risk of Bias Assessment Tool for Nonrandomized Studies [RoBANS], Assessing the Methodological Quality of Systematic Reviews [AMSTAR] for systematic reviews). For the systematic reviews, two reviewers undertook all review processes independently, except for data extraction where a second reviewer checked all of the data extraction sheets. For the rapid review 20% of all review processes were repeated and cross-checked by a second reviewer. In all cases, disagreements between reviewers were resolved by consensus or through discussion with a third reviewer.

Study design, treatment, population, and outcome characteristics were summarised in text and tables. Pooling study results by meta-analysis was only performed for the risk of EOGBS by different GBS serotype colonisation in neonates.

Results

The condition – condition, epidemiology, and natural history (key questions 1-15)

UK NSC criterion 1: *"The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease."*

Eighteen studies including two published reports from PHE and preliminary data from MBRRACE-UK and BPSU reported on the condition, epidemiology, and natural history questions.

- According to the most recent enhanced active national surveillance data available from the BPSU, the overall incidence of EOGBS was 0.57 per 1,000 live births in the UK and the Republic of Ireland over a 13-month period in 2014/2015. EOGBS incidence in England and Wales was inversely associated with gestational age at birth decreasing from 4.42 in 1,000 live births before 28 weeks of gestation to a rate of 0.41 in 1,000 live births after 37 weeks of gestation.
- The BPSU surveillance reported that risk factors based on NICE and RCOG guidelines were present in 41.3% and 35.4% of EOGBS cases, respectively, but only 44% of those with RCOG risk factors were treated with IAP. Approximately 22% (94/429) of EOGBS cases were in preterm deliveries. The percentage of babies with EOGBS born at term to mothers without any RCOG or NICE risk factors was 63-67% (n=212-225/335). This is the cohort that universal screening would try to detect. It decreased to 40% (133/335) if prolonged rupture of membranes (PROM >18 hours) was also added to the current UK risk-based guidelines.
- The reported EOGBS case fatality rate from the BPSU study was 5.2% in the UK and the Republic of Ireland in 2014/2015. Prematurity was an independent risk factor for death. Thirty-seven percent (10/27) of EOGBS deaths had at least one RCOG risk factor for GBS; only one mother of the 27 EOGBS babies who died received IAP. There were 10 deaths in babies with EOGBS born after 35 weeks' gestation; 60-70% (6/10 to 7/10) of them did not have any maternal risk factors based on RCOG and NICE risk factors. It is the death in these babies that universal GBS screening would try to prevent. It decreased to 50% (5/10) if PROM >18 hours was added to the current UK risk-based strategy. For babies born after 37 weeks, the number without any maternal risk factors was similar between 56% (5/9) to 67% (6/9) of EOGBS deaths, depending on risk factors included. A second study in Northern Ireland showed case fatality rate of 7% between 2008 and 2010.
- The GBS-related stillbirth rate was 4.0 per 100,000 total births in the UK in 2014; about half of the GBS-related stillbirths (16/31) occurred before 37 weeks of gestation.
- The concern with the BPSU and stillbirth data is that they are from approximately a one-year period, and it is unclear how these incidence, mortality, and risk factor figures fluctuate between years and how different this year may be compared to the others.
- Approximately 1% (31/3,215) of all stillbirths in the UK were attributed mainly or partly to GBS.
- GBS carriage status varied in pregnancy.
- Up to 33% of women with positive GBS-culture during their third trimester were GBS-negative at term and would be unnecessarily treated with antibiotics in a universal screening programme.

- Up to 12% of women changed from GBS-negative to positive and would miss out on IAP in a universal screening programme, unless they presented with GBS maternal risk factors.
- Approximately 58% of GBS-colonised women transmitted GBS to their neonates during labour when not treated with IAP. There are concerns of how applicable this figure is to the UK as this study was conducted in Gambia.
- Between 0.5% and 6% of colonised neonates developed EOGBS disease.
- There was little evidence on the long-term outcomes of babies with EOGBS, especially babies who were less severely affected.

The systematic review of 19 studies found

- The pooled comparison of serotypes in GBS colonised neonates showed a trend towards serotype III being more associated with EOGBS than all of the other serotypes. EOGBS was 1.5 times higher in serotype III than in serotype Ia and almost two times higher than serotype II.
- Bacterial load was associated with GBS vertical transmission from mother to neonate, and associated with EOGBS compared to asymptomatic GBS colonisation in neonates.
- Neonatal colonisation was approximately two to three times higher in mothers colonised with heavy GBS load compared to light GBS load.
- EOGBS was up to 15 times higher in neonates colonised with heavy GBS load compared to light GBS load.

However, these studies in the systematic review were at high risk of bias, particularly in the domains of study participation and confounding variables, where none of the included studies were at low risk of bias.

Overall, EOGBS is an important health condition, however, the natural history and the development from GBS carriage to EOGBS disease remain poorly understood. Therefore this criterion is not met. Research is required to fill this evidence gap on why mothers transmit GBS and why neonates develop EOGBS disease.

Criterion 1: Not met

The test (key question 16 and 17)

UK NSC criterion 4: *"There should be a simple, safe, precise and validated screening test."*

Six cohort studies were included in this review. The number of women included in the analysis of the predictive value of an antenatal culture GBS screening test at 35-37 weeks' gestation ranged from 53 to 289 in five studies and was unclear in one study. Risk of bias was considered high in two or more domains in three of six studies and in one domain in one study. Two studies did not receive a high risk of bias rating but were still judged as unclear risk of bias in one and two domains, respectively. Concerns regarding the applicability of the studies to the UK context were unclear or high in all studies because of one or more of the following reasons: ethnicity of the study population was non-UK or not reported, swab site and/or the culture medium used were not reported, the reference standard for intrapartum GBS carriage was performed up to seven days prior to delivery or swab site and/or culture medium was not reported, and the diagnostic methods for EOGBS were not reported or included GBS positive urine culture.

- Four included studies found that GBS carriage results changed between culture testing at 35-37 weeks and labour in 11% to 28% of screen-positive women and 5% to 9% of screen-negative women.
- Using a combination of studies that estimate each point in the natural history pathway, this review estimates that approximately 0.2% of mothers with an antenatal culture positive screening test result at 35-37 weeks and no IAP have a neonate with EOGBS. However, this figure contains large uncertainties due to the uncertainty present in the estimate for each point in the pathway. Using the number of term EOGBS cases found in the BPSU study against population figures, also gives an estimate of approximately 0.2%, even assuming perfect test accuracy. The only studies directly measuring this since the last review had large 95% confidence intervals from 0.4-40%, so are not very informative.
- Screening at 35-37 weeks is not a good predictor of GBS carriage in labour, GBS transmission to neonates, or EOGBS disease.
- Screening at 37 weeks would miss preterm births, which are at a higher risk of EOGBS and its most severe consequences.

Criterion 4: Not met

The treatment (key question 18-20)

UK NSC criterion 9: *"There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered."*

The effectiveness of IAP questions related to UK NSC criterion 9 were addressed in eight studies. Five studies were cohort studies; three of them were prospective and two were retrospective. Among the remaining three studies was one uncontrolled before-after study with retrospective data collection, one secondary analysis of a multistate cohort with propensity score matching and one update of a systematic review. Five of the seven included primary studies had another focus but provided data on the number of EOGBS cases in GBS-positive women who received or did not receive IAP, which are described narratively only. Risk of bias was considered high in two or more domains in four of the seven observational studies (57%) and in one domain in the remaining three studies (43%). No study was judged as low or unclear risk of bias in all six domains. Confounding variables was the area with the greatest risk of bias (5/7, 71% high risk), as confounding factors were not adequately considered during the design and analysis. Another issue was that outcome assessments were not blinded in all seven studies; depending on the outcome, the risk of detection bias was judged as high in three studies. The risk of bias in the included systematic review received an AMSTAR score of 9/11, which indicates a high methodological quality (AMSTAR score 9 – 11) of this paper.

- Compared to no treatment, one new observational study found that IAP using penicillin/ampicillin for at least four hours reduced the risk of culture-proven EOGBS by 89%, while the update of a systematic review of RCTs included in the previous review found that IAP reduced it by 83%. However, these results might be biased as RCTs were small, old, and at high risk of bias, while the observational findings could have been affected by selection bias.

- The two observational studies found that the effectiveness of IAP is reduced in women who receive IAP for less than four hours (adjusted relative risk for neonatal clinical sepsis 2.9, p=0.01, compared to IAP of at least four hours) or who receive IAP with clindamycin due to reported penicillin allergy (p=0.47 compared to no treatment). However, the evidence is from studies that have a high risk of bias.

There is even greater uncertainty about the potential harms of IAP: The systematic review of 26 studies showed a wide range of harms that could occur in mothers and children as a result of IAP, but all evidence either had limited applicability to the question (for example using different antibiotics) or had high risk of bias (which may have biased results).

- Observational studies found microbiota changes, maternal thrush, neonatal respiratory distress, and increased length of stay in women and babies who received IAP. These studies were most applicable, as some explicitly included IAP for GBS prevention. However, these were observational studies at high or unclear risk of bias, and results could be due to confounding variables.
- RCT evidence is the least biased method of measuring harms. One RCT that had the lowest risk of bias found that mothers treated with IAP for preterm labour (erythromycin or co-amoxiclav), were more likely to have children suffering from cerebral palsy compared mothers not treated with erythromycin or co-amoxiclav. Mothers treated with erythromycin only, were more likely to have children who would suffer from mild functional impairment and bowel problems, compared to women not treated with erythromycin. However this trial has limited applicability as it used a different drug, a longer drug regimen, and pre-term rather than term labour, so we do not know whether these or similar effects would be found in IAP after screening for maternal GBS carriage. Furthermore, multiple analyses were conducted on a relatively small sample, so this result may simply be due to chance, and the plausible biological mechanisms through which IAP can cause the development of cerebral palsy are unknown.
- Other potential harms included asthma, colonisation or infection with ampicillin resistant organisms, maternal thrush, childhood atopic dermatitis, microbiota changes, neonatal infections, necrotising enterocolitis, respiratory problems, or *Clostridium difficile* bowel problems. However, this evidence was inconsistent and/or at high risk of bias.
- Therefore, the best quality RCT evidence on the harms from IAP, with the lowest risk of bias, had low applicability, and the most applicable evidence that explicitly included GBS prophylaxis, was at high risk of bias.

Better quality evidence is needed to address the effectiveness and adverse events from IAP as both are uncertain, although the reviewers recognise the difficulty in conducting an RCT when IAP has become the recommended treatment.

Criterion 9: Not met

The screening programme – clinical effectiveness (key question 21)

UK NSC criterion 11: *"There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity."*

The effectiveness of antenatal screening for maternal GBS carriage related to UK NSC criterion 11 was addressed in three studies. There were no randomised controlled trials of offering screening in

comparison to not offering screening. All three studies were observational studies using historical controls and comparing the rates of EOGBS in different periods of time in which different GBS prevention strategies were used. The control periods (no screening and/or risk-based approach) preceded the universal screening periods in all included studies. Risk of bias was considered high in two or more domains in all three studies (100%). Selection of participants and confounding variables were the areas with the greatest risk of bias (3/3, 100% high risk for both areas) as participants of study and control period were not contemporaneous, data were collected retrospectively in two studies and confounding factors were not adequately considered during the design and analysis in any study. Screening strategy, risk-based strategy, and IAP treatment regime in the two studies from the USA were not described; therefore the applicability to the UK is unclear, as well as the applicability to the question of a screening programme specifically at 35-37 weeks, using only enriched vaginal and rectal culture. One study from Hungary performed antenatal GBS screening earlier than 35-37 weeks (at 30-32 weeks of gestation); the applicability of the results for a GBS screening programme in the UK performed at 35-37 weeks of gestation is therefore reduced. Two of the three studies reported experiences from a single centre only; it is therefore unclear if the reported results are generalisable to the whole population. Reported outcome in the remaining study was the number of EOGBS cases per 1,000 admissions to 322 neonatal intensive care units (NICUs) in the US; the impact of universal GBS screening and IAP for the whole population of live born babies is therefore unclear. Furthermore, in all three included studies, the EOGBS definition included urine culture and the method of obtainment for urine was unclear in two studies (collection by catheter reduces risk of contamination).

- All three observational studies consistently report a decreased incidence of EOGBS with universal GBS screening compared to the era without any GBS screening, but reported benefits compared to the era with a risk-based approach are inconsistent.
- One USA study found lower odds of developing EOGBS using multivariate regression (OR 0.69; $p<0.001$) in the period with universal GBS screening compared to the period with a risk-based approach (denominator in this study were all admissions to 322 NICUs).
- Findings from the other USA study suggested that the incidence of culture-proven EOGBS decreased after introduction of a risk-based approach (from 2.06 per 1,000 live births with no formal IAP guideline to 0.96 per 1,000 live births with risk-based approach) but was not further reduced in the era of universal GBS screening (1.11 per 1,000 live births). Details of the risk factors that resulted in IAP administration in the risk-based approach were not reported in the paper. Therefore, the applicability to the UK is unclear.
- The difference between the study results may be due to differences in the setting and population studied as well as the difference in the EOGBS definition.
- Results on the impact of universal GBS screening on EOGBS mortality are also inconsistent.
- The two studies conducted in the USA did not find a change in the EOGBS mortality rate or mortality rate from all early-onset infections between periods with and without universal GBS screening while the Hungarian study reported decreased EOGBS mortality rates after introduction of universal GBS screening compared to no screening.

As no RCTs were found in this update review and only three observational studies were available that were all at high risk of bias, it remains difficult to assess the impact of implementing a universal screening programme for GBS carriage in pregnancy. An RCT on the effectiveness of universal screening for GBS carriage in pregnancy on neonatal sepsis less than seven days would answer this question.

Criterion 11: Not met

The screening programme – cost effectiveness (key question 22)

UK NSC criterion 14: *"The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource."*

No new evidence on the cost effectiveness of antenatal culture screening for maternal GBS carriage was found. The previous review reported that the criterion was not met, as they found no new cost-effectiveness estimates relevant to the UK. The review before that concluded that there are aspects to screening for GBS, which are not easy to incorporate in a cost-effectiveness model, such as *"the effect of widespread use of antibiotics on the development of antibiotic resistance and the impact this will have; the impact of increased medicalisation of birth on maternal and neonatal outcomes; and the effect of very rare but potentially catastrophic anaphylaxis in labour."*

Criterion 14: Not met

Conclusions and implications for policy

This review has found that

- GBS is an important health problem, but all five investigated UK NSC criteria are not met.
- Applying the identified estimates from 2014/2015 for the UK to a hypothetical cohort of 776, 352 pregnant women, GBS causes at least 31 stillbirths. EOGBS affects 97 premature babies per year, of which 15 die. EOGBS affects 346 term babies, of which 10 die. In those term babies who die from EOGBS, three have maternal risk factors so delivery could be managed by current risk-based strategies. There are 219-233 term babies born with no maternal risk factors who develop EOGBS, (of which seven die), that is the cohort which universal GBS screening would try to detect.
- The proposed screening programme would offer approximately 718,126 term pregnant women (≥37 weeks) the antenatal GBS culture test. Women with preterm birth would miss the opportunity for screening. Assuming all 718,216 pregnant women accepted screening, 150,806 would be positive and offered IAP. Of these 150,800, only 0.2% (333/150,806) would have a baby with EOGBS without IAP. Therefore approximately 99.8% (150,467) of screen-positive and treated mothers (and their babies) would be over-treated.
- A strong relationship was found between bacterial load and GBS transmission from maternal to neonatal GBS colonisation, and between bacterial load and EOGBS compared to asymptomatic colonisation in neonates.
- Serotype III was also more associated with EOGBS compared to serotype Ia and II. There were no other significant differences between the serotypes in the meta-analysis.
- It is still not fully understood why some mothers, but not others, transmit GBS to their neonates, or which neonates will develop the disease.
- Fifty-nine to 65% of EOGBS cases did not have any clinical risk factors for GBS based on current UK prevention guidelines. In those with RCOG risk factors, only 44% had received IAP; 50% of which received IAP for less than two hours. Ten to 13 mothers (37-48%) whose baby died from EOGBS had at least one risk factor based on current UK prevention guidelines, but only one of these women was treated with IAP.

- The evidence in this report is consistent with the previous review's conclusion that selective culture at 35-37 weeks gestation is not an accurate predictor of colonisation status in labour, transmission of GBS, or EOGBS disease in the neonate.
- Based on these results, a substantial proportion of women would be unnecessarily treated with IAP if a universal screening programme were introduced.
- There may be potential harms from IAP, however, the evidence on this is inconsistent, and at high risk of bias, and therefore uncertain.

Research needs

- The risk factors used in the risk-based prevention strategy could be explored with the aim of identifying more EOGBS cases, and treating fewer women whose babies would not go on to develop EOGBS. The reasons for the low adherence to the risk-based prevention policy should be investigated as only 44% of EOGBS cases with RCOG risk factors are treated with IAP.
- We do not know the balance of benefits and harms of introducing universal antenatal culture screening in addition to risk-based prevention. To measure these would require RCT evidence, with economic modelling to evaluate the associated costs. However, it is estimated that 0.2% of women who test positive for GBS in the third trimester would go on to have a baby with EOGBS.The positive predictive value of such a screening programme would be very low and overtreatment high.
- To improve the balance of benefits and harms for future proposed screening programmes more research is needed to understand the natural history of GBS, which could help to identify the women who are at most risk of transmitting GBS to their neonates, or the colonised neonates who are at most risk of developing EOGBS. This could help to reduce the number of women treated with antibiotics who are at low risk of having neonates with EOGBS. Although this research is required and is worth exploring, it may be not identify any detectable factors above the current known risk factors that could be used to change practice on who receives prophylaxis. The particular recommendations are:
    - Research to reliably predict which mothers with GBS during labour will transmit GBS to the neonate (approximately 58% of GBS positive women in labour will transmit to the neonate) and which mothers will have a neonate that develops EOGBS. The characteristics may include clinical or demographic risk factors in the mother, biochemical or molecular markers, or bacterial load.
    - Research to reliably predict which neonates with GBS colonisation will progress to EOGBS disease (even without IAP only 0.5% with GBS colonisation might progress to EOGBS disease). Similar to above, characteristics may include clinical or demographic risk factors, biochemical or molecular markers, or bacterial load. It may be difficult to identify neonates with GBS colonisation who will progress to EOGBS in a timely and highly accurate manner to rule out the approximately 99% of neonates with colonisation who do not go on to disease. Nevertheless, there may be infant characteristics that give some prediction. However, they would have to offer strong negative predictive value to justify not treating positive infants.
    - Test accuracy research to reliably detect GBS colonisation and bacterial load during labour (approximately 27% of GBS positive women at 35-37 weeks were negative during labour, and 5% of GBS negative women at 35-37 weeks were positive during labour). Although the latest in-labour tests may have some practical issues, there may be a feasible option to more accurately measure who is colonised in labour and how heavily.

- Evidence is needed to understand the burden of GBS associated with stillbirth. As this is a burden not amenable to interventions in labour, interventions earlier in pregnancy may be required.

1. Introduction

Health problem

Group B *Streptococcus* (GBS), or *Streptococcus agalactiae* is a naturally occurring gram-positive bacterium that colonises the gastrointestinal and genitourinary tract in approximately 30% of healthy adults.[1-3] Globally, GBS carriage in pregnant women varies, and in developed countries it has been retrieved from vaginal and/or rectal swabs in between 10% and 30% of tested women.[4,5] If a pregnant woman carries GBS when she is in labour, it has been reported that there is a 36% chance that GBS will be transmitted to her neonate.[6,7] The majority of the neonates with GBS colonisation will be asymptomatic. However, 1% will suffer from invasive GBS disease,[8] and up to 10% of those affected by invasive GBS will die from the infection.[9,10]

Invasive neonatal GBS disease is separated into early-onset GBS (EOGBS) and late-onset GBS (LOGBS). EOGBS occurs during the first seven days of life, with approximately 90% of cases presenting within 24 hours.[10] While maternal colonisation is thought to be the direct cause for EOGBS, LOGBS can be transmitted from other sources.[8] EOGBS cases progress rapidly, presenting with sepsis in 63% of cases or pneumonia in 26%.[6,10] EOGBS can cause meningitis, which, though rare, is associated with long-term neurodevelopmental defects in half of neonates presenting in this way.[3,11,12]

Intrapartum antibiotic prophylaxis

The current recommendation for intrapartum antibiotic prophylaxis (IAP) is intravenous penicillin (or ampicillin in the US) given as soon as possible after the onset of labour and then every four hours until delivery.[13,14] Second-line treatment for mothers allergic to penicillin varies across countries. In the UK, intravenous clindamycin is recommended,[13] whereas in the US, intravenous cefazolin is the first alternative, followed by clindamycin if there is a history of anaphylaxis, angioedema, respiratory distress, or urticaria after penicillin or cephalosporin.[14]

Prevention approaches

Different strategies are used across countries to identify women at risk of having a baby with EOGBS, in order to treat them with IAP. In the UK,[13,15] Netherlands,[16] and New Zealand,[17] risk-based prevention is recommended. In the UK, women who present with risk factors (i.e. maternal GBS carriage, bacteriuria or infection, pre-term pre-labour rupture of membranes, intrapartum fever, previous infant with invasive GBS disease, and chorioamnionitis)[13,15] are offered IAP in labour. There are currently no high quality studies on the effectiveness of risk-based prevention in the UK. Based on 2012 voluntary laboratory reporting data and clinical network data, it appeared that under risk-based screening in the UK, GBS incidence had remained at just below 0.5 per 1,000 live births.[18,19] A criticism of this approach is that approximately 30% of cases without risk factors are excluded from prevention.

As GBS maternal carriage is a pre-requisite for EOGBS disease,[8] an alternative approach to increase the detection of GBS carriage in pregnant women is universal antenatal screening. This involves culturing rectal and/or vaginal swabs from all pregnant women and offering IAP to those with positive results. As culture tests take 24 to 48 hours to process, culture screening cannot be offered at the point of prophylactic treatment in labour, as results would not be available in time to treat. Therefore, 35-37 weeks has been selected as the time to test for GBS using culture, as it balances the changes in colonisation status with sufficient time to obtain results.[14]

Concerns about increased antibiotic resistance,[20,21] increase in neonatal infections caused by gram-negative bacteria as a result of selection pressure on the organisms causing infection,[7,22] and other potential harms have been raised. A predisposition to *Clostridium difficile* infection,[23] changes in the neonatal microbiota leading to long-term health problems, maternal anaphylaxis,[14] and increased medicalisation of labour[7,13] have also been raised as possible harms.

Basis for current recommendation

In 2003, 2008 and 2012, the UK NSC reviewed the evidence for universal screening.[24] The reports concluded that universal screening of pregnant women for GBS should not be offered, as there was insufficient evidence to ensure that the benefits of screening and IAP would outweigh the harms.

Current update review and approach taken

UK NSC screening reviews are updated every three years, and the GBS review is currently due. The purpose of this review was therefore to update the 2012 review on the scientific evidence on GBS that has been published in the last four years. This review will inform discussion and decision-making about further work on the viability of universal GBS screening, for example primary research, cost effectiveness analysis, and disease modelling.

2. Research aims

The aim of this review was to update and summarise the evidence on the key issues for universal antenatal culture screening for GBS carriage, since the last UK NSC review in 2012. This update review investigated whether there have been any significant developments in the evidence base on key questions identified in the last UK NSC review. These were; the incidence, epidemiology, and natural history of GBS, the diagnostic accuracy of culture tests, the treatment for GBS maternal colonisation, and the clinical- and cost- effectiveness of a GBS screening programme. The key clinical questions considered in this review that address the UK NSC criteria on the condition, the test, the treatment and the screening programme, are shown below. Questions nine and 10 (GBS-related stillbirths), question 15 (GSB bacterial load and molecular markers), and question 20 (adverse events from IAP) are new questions that have not previously been reviewed.

The condition

UK NSC criterion	Key questions
Condition and Epidemiology	
1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	1. What is the overall incidence of EOGBS in the UK?
	2. What is the distribution of EOGBS by maternal risk factors in the UK?
	3. What is the clinical presentation of EOGBS in the UK?
	4. What is the overall mortality rate attributable to EOGBS in live born babies in the UK?
	5. How is the mortality attributable to EOGBS distributed by maternal risk factors in the UK?
	6. What short-term morbidities are associated with EOGBS in the UK?
	7. What proportion of EOGBS cases has long-term mild or severe morbidities?
	8. What is the association between EOGBS clinical presentation and morbidity outcomes?
	9. What proportion of stillbirths is associated with GBS each year in the UK, and does this reliably contribute to estimates of GBS associated mortality?
	10. What is the relationship between gestational age and GBS-related stillbirths in the UK?
Natural history	
1. The condition should be an important health problem as judged by its	11. What is the maternal GBS carriage rate in the UK?
	12. What proportion of antenatal screen positive and screen negative women

UK NSC criterion	Key questions
frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	transition in terms of carriage status at term?
	13. What proportion of screen positive women at term transmits the bacterium to the baby?
	14. What proportion of colonised babies is affected by EOGBS?
	15. Are there bacterial loads and/or bacterial molecular markers predictive of GBS transmission (from maternal colonisation to neonatal colonisation or EOGBS disease) or GBS transition (from neonatal GBS colonisation to EOGBS disease)?

The test

UK NSC criterion	Key questions
4. There should be a simple, safe, precise and validated screening test.	16. What is the sensitivity and specificity of selective antenatal culture screening tests?
	17. What is the predictive value of selective antenatal culture screening tests for a) carriage status at term and b) EOGBS disease?

The treatment

UK NSC criterion	Key questions
9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	18. What is the reported effectiveness of IAP in preventing EOGBS related morbidity and mortality in screen-detected populations?
	19. What is the reported effectiveness of IAP in preventing culture negative/probable EOGBS in screen-detected populations?
	20. What adverse events do women or children experience after receiving IAP treatment for any prophylactic reason?

The screening programme

UK NSC criterion	Key questions
11. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity.	21. What is the clinical effectiveness of GBS screening on EOGBS-related mortality and morbidity, neonatal sepsis and neonatal sepsis-related mortality?
14. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.	22. What is the cost effectiveness of GBS screening in the UK?

3. Methods

Two different methods were used for this review. For question 15 (GBS bacterial load and molecular markers) and question 20 (adverse events from IAP), full systematic review methodology was applied, as these were new questions that have not been previously reviewed in the literature. For the remaining questions, a rapid evidence assessment (REA) approach was used. The UK NSC has produced a set of requirements for REAs, for use in its evidence review process. This provided the reference point for the conduct of the review; for example, this means that a second reviewer for the rapid review checked 20% of sifting, data extraction and quality appraisal. In the systematic review, on the other hand, the whole process was duplicated. Any disagreements were resolved through discussion or through involvement of a third reviewer. An iterative approach was adopted to formulate and refine the research questions and scope of the review by seeking guidance from all authors and the UK NSC.

3.1 Identification of studies

Search strategy for rapid review (question 1-14, 16-19, 21-22)

One broad literature search using various GBS terms was performed to encompass all of the clinical questions. The search was developed for Medline and adapted for the remaining databases. Articles were limited to the English language, humans, and publication from 2012 onwards (the date of the last search was February 2012). Searches were conducted on 21 April 2016 in MEDLINE (Ovid); MEDLINE In-Process & Other Non-Indexed Citations (Ovid); EMBASE (Ovid); and the Cochrane Library: Cochrane Database of Systematic Reviews, CENTRAL, DARE and HTA databases (Wiley). The search strategies developed for Medline are provided in **Appendix 1**.

In addition to the electronic databases, published reports from PHE and unpublished data from the British Paediatric Surveillance Unit (BPSU) were searched for questions 1-6 and 8; unpublished data from Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries (MBRRACE-UK) were used for questions 4, 9, and 10.

Experts (as identified by the UK NSC) reviewed the final list of included studies to identify any articles not captured by the search.

Search strategy for systematic reviews (questions 15 and 20)

The search strategy for the systematic reviews comprised searching of electronic bibliographic databases, scrutiny of references of included studies and relevant systematic reviews, and contact with experts in the field as identified in discussion with the UK NSC. The search strategy was developed using an iterative process, with input from all authors, recommended search filters,[25,26] and the previous UK NSC review.[24] For question 15, the search combined terms for GBS, neonate and pregnancy, and terms for bacterial load and molecular markers. For question 20, search terms for antibiotic prophylaxis, labour, and adverse events including terms for known adverse events from IAP (such as antibiotic resistance or maternal anaphylaxis) were combined. The search was limited to antibiotics for prophylactic purposes during labour. Strategies for both searches were limited to the English language and humans (see **Appendix 1** for strategies). Searches were conducted on 6 May 2016 on MEDLINE (Ovid); MEDLINE In-Process & Other Non-Indexed Citations (Ovid); EMBASE (Ovid); Cochrane Library: Cochrane Database of Systematic Reviews, CENTRAL, DARE and HTA databases (Wiley); and Science Citation Index Expanded (Web of Science).

3.2 Selection of studies

Inclusion criteria for rapid review (question 1-14, 16-19, 21-22)

The detailed inclusion criteria for each review question are shown in **Appendix 2**. To summarise, papers that met one of the following criteria were included for a certain review question:

Review question	Inclusion criteria
1-14	Papers on the epidemiology or natural history GBS carriage in pregnant women in their third trimester onwards, GBS carriage in newborn babies less than seven days, or GBS disease in stillborn babies or newborn babies less than seven days.
16/17	Papers on the test accuracy of selective culture from recto-vaginal swabs in pregnant women ≥35 weeks compared to selective culture from recto-vaginal swabs in full term labour to diagnose GBS carriage in full term labour or culture confirmed EOGBS disease (less than seven days from a sterile site).
18/19	Papers on the effectiveness of intrapartum antibiotic prophylaxis on culture-confirmed EOGBS (sepsis, pneumonia, meningitis, death from culture-confirmed EOGBS less than seven days) or negative/probable EOGBS (symptoms or signs of sepsis, pneumonia or meningitis with negative GBS culture from a sterile site less than seven days, but mother is GBS positive) compared to no treatment or placebo.
21	Papers on the effectiveness of GBS screening in pregnant women in the third trimester: selective culture from recto-vaginal swabs and IAP treatment of women with positive results. Outcomes were culture-confirmed EOGBS (sepsis, meningitis, pneumonia, or death from culture-confirmed EOGBS less than seven days from a sterile site) or culture negative/probable EOGBS and related death (symptoms or signs of sepsis, pneumonia or meningitis with negative GBS culture from a sterile site less than seven days, but mother is GBS positive), or early-onset sepsis and related death (culture-confirmed from sterile site and/or culture negative with symptoms only less than seven days) compared to no screening.
22	Papers on the cost-effectiveness of screening pregnant women in the third trimester with antenatal selective culture from vaginal or rectal swabs and treating those with positive results with IAP compared to no screening as measured by life years, quality of life years, deaths avoided, or disease avoided.

Systematic reviews, cross-sectional studies, cohort studies, case-control studies, randomised controlled trials, and economic evaluations with incremental cost-effectiveness ratios (ICERs) were included. Published reports from PHE and the BPSU, as well as unpublished data from MBRRACE-UK were

included for questions 1-10. For questions 1-10 and 21, studies needed to have regional or national coverage.

Studies outside the UK were excluded for questions 1-6, 9-10, 11, and 22. Papers not in the English language or published before February 2012 (date of last search) as well as letters, editorials, communications, case reports, case series, and abstracts were also excluded.

Inclusion criteria for systematic reviews (questions 15 and 20)

Studies that satisfied the following criteria were included into the systematic reviews:

	Question 15	**Question 20**
Population	Colonised mothers or neonates who did not receive IAP	Mothers or children of mothers having received IAP only for prophylactic purposes other than caesarean section and surgical prophylaxis
Outcome	Association between bacterial loads or individual bacterial molecular markers and the development of neonatal GBS colonisation or neonatal early-onset GBS disease	Any adverse outcomes experienced by mother or child, after asymptomatic women were given IAP for prophylactic purposes
Study design	Prospective or retrospective cohort studies, and nested case-control studies	Prospective or retrospective cohort studies, case-control studies, or randomised controlled trials

Detailed inclusion criteria can be found in **Appendix 2**.

Case series and case reports were excluded from both reviews, as there was sufficient data from studies that compared the study group to controls. Without control groups, it is impossible to infer whether adverse events are caused by, or associated with, IAP or not. Likewise, it is impossible to infer whether the bacterial marker or degree of bacterial load is present more often in participants with GBS transmission or EOGBS, compared to those without. Any papers not in the English language as well as letters, editorials, communications, and abstracts were excluded.

3.3 Review strategy

Titles and abstracts of all identified bibliographic records were screened using pre-defined inclusion and exclusion criteria and all potentially relevant studies were taken forward for full text screening using the same criteria. Records rejected at full-text stage and reasons for their exclusion were documented (**Appendix 9**,**Appendix 10** and **Appendix 11**).

3.4 Data extraction strategy

Information was extracted from included studies using electronic piloted data extraction forms. An example of the data extraction sheets is provided in **Appendix 3-A** and **Appendix 3-B/C**.

3.5 Quality assessment strategy

Methodological quality of studies included in the rapid review was assessed for the questions on test accuracy, IAP treatment effectiveness, screening clinical and cost effectiveness (questions 16-19 and 21-22). For the studies on test accuracy, questions (questions 16 and 17), an unadjusted QUADAS-2 tool[27] was used (see **Appendix 4-A**). For questions on the effectiveness of IAP and GBS screening (questions 18, 19, and 21), the quality of non-randomised studies was assessed using the Risk of Bias Assessment Tool for Nonrandomised Studies (RoBANS)[28] (**Appendix 4-C**), while the quality of systematic reviews was appraised using A Measurement Tool to Assess Systematic Reviews (AMSTAR)[29](**Appendix 4-E**).

Studies included in the systematic reviews were assessed using the Quality in Prognosis Studies (QUIPS) tool[30] (**Appendix 4-D**) (Question 15), the Cochrane Risk of Bias (RoB)[31] tool for RCTs (**Appendix 4-B**) and the Risk of Bias Assessment Tool for Nonrandomised Studies (RoBANS)[28] (**Appendix 4-C**) (Question 20).

3.6 Methods of synthesis

For the rapid review, study design, treatment, population, and outcome characteristics were summarised in text and tables. In addition, by linking each question to the UK NSC criteria, an overall statement of the quality of evidence as it relates to the data was made. The evidence for each criterion assessed was classified as 'met', 'not met' or 'uncertain' as required by the UK NSC,[32] and compared to the statement for each criterion in the previous review. Pooling of study results through meta-analysis was not performed.

For the systematic reviews, meta-analyses were only conducted on the serotypes predictive of transition from neonatal colonisation of GBS to EOGBS. The random effects model[33] was used due to anticipated between-study differences in the methods, EOGBS definitions, and countries where studies were conducted. As there were no summary measures reported in the studies, the relative risk (or risk ratios) along with 95% confidence intervals (CI) were calculated for each study and pooled. The heterogeneity was assessed using forest plots, the chi-squared test for heterogeneity with a 10% level of statistical significance, and using the I^2 statistic where a value of 50% is represented as moderate heterogeneity.[34,35] Comparisons were only made for serotypes that were included in at least two studies.

Meta-analyses could not be performed for the systematic review investigating the adverse events from IAP (question 20), due to the extensive heterogeneity across the adverse outcomes assessed. They could also not be conducted for the systematic review on the remaining bacterial molecular markers or the bacterial load predictive of neonatal colonisation of EOGBS, due to the heterogeneity in the markers and the definitions of bacterial load. The characteristics of the studies and the results for these data were summarised in text and tables. For studies where relative summary measures were not reported, they were calculated by the authors and indicated as such. Odds ratios were calculated for case-control studies and relative risks (or risk ratios) were calculated for all other study designs.

4. Results: Appraisal against UK NSC criteria

The full list of the UK NSC criteria is available online at: https://www.gov.uk/.

4.1 Overall description of the evidence

Rapid review (questions 1-14, 16-19, 21-22)

The electronic search resulted in 2,912 references; four further references were identified from surveillance websites (two from PHE, one from BPSU and one from MBRRACE-UK). No additional references from expert suggestions were included. After sifting through titles and abstracts, 208 full text articles were assessed of which 180 were subsequently excluded using the pre-defined inclusion/exclusion criteria (see **Appendix 9** for excluded studies with reason). This left 28 articles, which met the inclusion criteria, and were included in the narrative synthesis. **Appendix 5** provides the PRISMA diagram for all included papers as well as the papers included for each criterion. Matching of included papers to the 20 individual key questions is shown in **Appendix 6**.

Systematic review on the bacterial load and bacterial markers of GBS transmission/transition (questions 15)

The search resulted in 1,070 unique references. After sifting titles and abstracts, 66 full text articles were assessed, of which 47 were subsequently excluded using the pre-defined inclusion/exclusion criteria (see **Appendix 10** for excluded studies with reason). This left 19 articles that met the inclusion criteria, and these were included in the synthesis. **Appendix 7** provides the PRISMA diagram for question 15.

Systematic review on the adverse events from IAP (question 20)

The search resulted in 2,305 unique references. After sifting through titles and abstracts, 253 full text articles were assessed, of which 227 were subsequently excluded using the pre-defined inclusion/exclusion criteria (see **Appendix 11** for excluded studies with reason). This left 26 articles that met the inclusion criteria, and these were included in the synthesis. **Appendix 8** provides the PRISMA diagram for question 20.

4.2 Evidence on the UK NSC criterion addressing the condition, its epidemiology, and natural history (key questions 1-15)

1. What is the overall incidence of EOGBS in the UK?
2. What is the distribution of EOGBS by maternal risk factors in the UK?
3. What is the clinical presentation of EOGBS in the UK?
4. What is the overall mortality rate attributable to EOGBS in live born babies in the UK?
5. How is the mortality attributable to EOGBS distributed by maternal risk factors in the UK?
6. What short-term morbidities are associated with EOGBS in the UK?
7. What proportion of EOGBS cases has long-term mild or severe morbidities?
8. What is the association between EOGBS clinical presentation and morbidity outcomes?
9. What proportion of stillbirths is associated with GBS each year in the UK, and does this reliably contribute to estimates of GBS associated mortality?
10. What is the relationship between gestational age and GBS-related stillbirths in the UK?
11. What is the maternal GBS carriage rate in the UK?
12. What proportion of antenatal screen positive and screen negative women transition in terms of carriage status at term?
13. What proportion of screen positive women at term transmits the bacterium to the baby?
14. What proportion of colonised babies is affected by EOGBS?
15. Are there bacterial loads and/or bacterial molecular markers predictive of GBS transmission (from maternal colonisation to neonatal colonisation or EOGBS disease) or GBS transition (from neonatal GBS colonisation to EOGBS disease)?

These questions relate to UK NSC criterion 1:

"The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease."

Description of the evidence

Eighteen studies including two published reports from PHE[36,37] and preliminary data from MBRRACE-UK[38] and the BPSU[39] reported on the condition, epidemiology, and natural history questions related to NSC criterion 1 (see **Appendix 6**). Seventeen studies were observational studies: six prospective cohort studies,[40-45] three retrospective cohort studies,[46-48]two prospective surveillance studies,[39,49] and six retrospective surveillance studies.[19,36-38,50,51] The remaining study was a systematic review.[52] Study details of all included studies are presented in **Appendix 12**.

The systematic review on the bacterial load or bacterial molecular markers predictive of GBS neonatal colonisation or EOGBS disease (question 15) resulted in 19 studies (see **Appendix *20***).[53-71] There was one case-controlled study,[56] one retrospective secondary analysis,[63] and the remainder were cohort studies. There were nine studies on vertical transmission of GBS colonisation,[53,55,58,61,62,64-67] five studies on maternal colonisation to EOGBS disease,[55,62,64,65,67] and nine studies on transition of neonatal GBS colonisation to EOGBS disease.[54,56,57,59,60,68-71] Thirteen studies were conducted before 1990,[54,55,57,58,60-

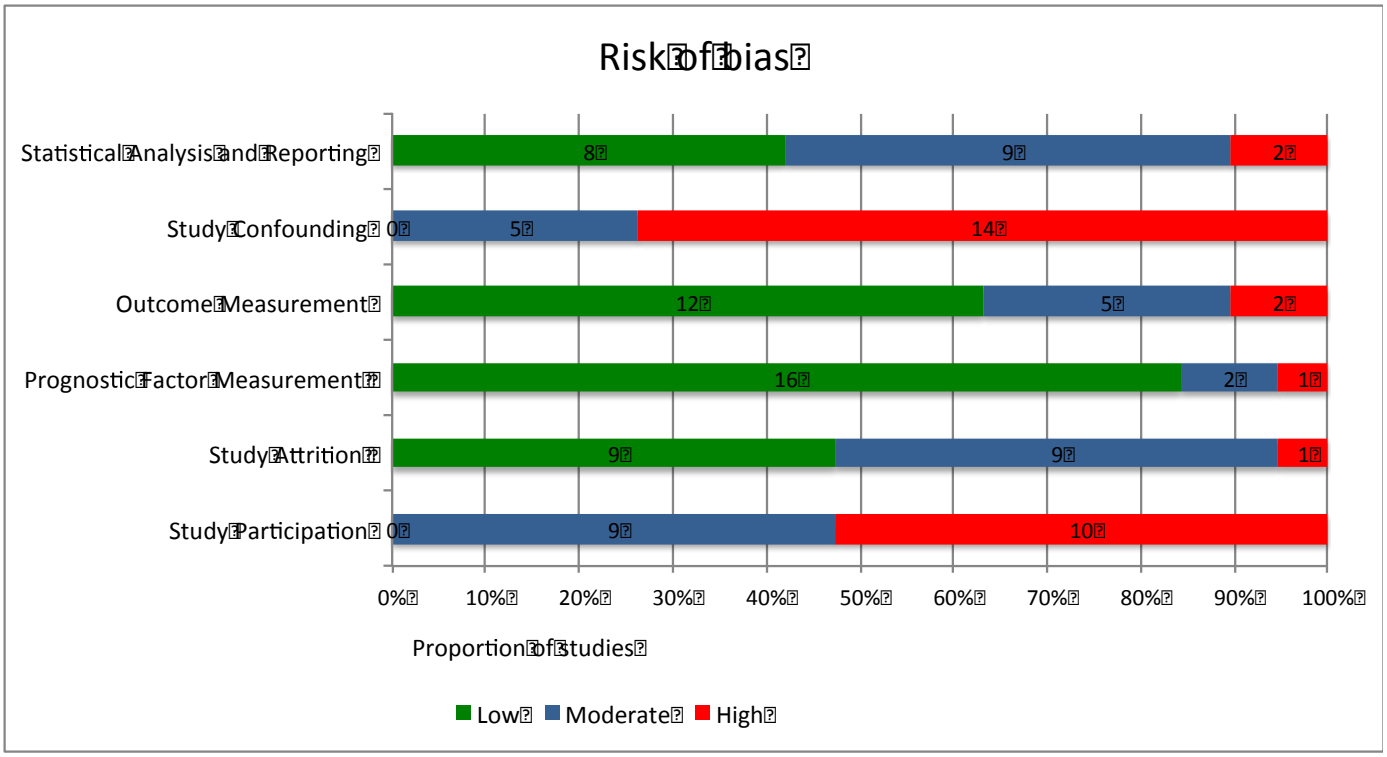
[62,64-66,68,69,71] two studies were conducted during the 1990s,[56,67] and four were conducted after 2000.[53,59,63,70]

Methodological quality of included studies

The methodological quality was not assessed for studies included for review questions 1-14.

Risk of bias judgements: Low= The study methods for the respective domain are unlikely to alter the results; Moderate= The study methods for the respective domain may alter the results; High= The study methods for the respective domain are likely to alter the results.

Figure 1 shows the overall methodological quality of the included studies for question 15, as assessed by the QUIPS tool.[30] Across the evidence, there was high risk of bias in the study participation and confounding variables domains, as none of the studies were at low risk of bias for either domain. Ten studies were at high risk of bias,[53-58,61-63,71] and nine studies were at moderate risk[59,60,64-70] for study participation, as baseline characteristics were not adequately described and/or recruitment methods were not fully stated. There was high risk of bias for confounding variables in 14 studies as they were not accounted for in study designs,[53,55-58,60-63,65,66,69-71] and moderate risk in the remaining five studies[54,59,64,67,68] as there was information in the studies about only some, but not other, confounding variables. For the statistical analysis and reporting domain, two studies were at high risk of bias,[58,61] and nine studies were at moderate risk of bias.[54-57,62-64,67,68]



Risk of bias judgements: Low= The study methods for the respective domain are unlikely to alter the results; Moderate= The study methods for the respective domain may alter the results; High= The study methods for the respective domain are likely to alter the results.

Figure 1. Risk of bias in studies addressing question 15, according to the QUIPS[30]

Analysis of the evidence

Regarding the importance of the health condition, the previous review[24] in 2012 concluded that EOGBS disease is an important health problem. They found that "*GBS remains the most common cause of early onset neonatal sepsis in England, estimating that it accounts for just over 50% of cases of sepsis that occur in the first 48 hours of life. According to the Health Protection Agency the overall incidence of EOGBS bacteraemia in England, Wales, and Northern Ireland in 2010 was 0.41 per 1,000 live births. Studies suggest that the case fatality rate among infants with EOGBS in the UK may be between 5% and 10%... about 31 neonatal deaths related to GBS in England, Wales, and Northern Ireland. This is broadly consistent with the BPSU study published in 2004, which found an overall rate of EOGBS across the UK and the Republic of Ireland the year 2000-2001 of 0.48 per 1,000 live births and a case fatality rate of 10.6% (377 cases of EOGBS overall and 38 deaths).*"

Regarding the natural history and the epidemiology, the previous review[24] in 2012 concluded, "*The natural history of GBS carriage in pregnant women remains only partly understood. It is known that GBS colonisation status as detected by antenatal culture at 35 to 37 weeks does not remain stable until the time of delivery in all women. Recent studies have reported that between about 30% and 40% of women found to be positive for GBS colonisation antenatally at 35 to 37 weeks' gestation are found to be negative for GBS colonisation at the time of labour. In addition between about 5% and 12% of women found not to carry GBS antenatally at 35 to 37 weeks' gestation are found to be positive by the time of labour. One study found that about 1% of women who are GBS culture negative during labour have infants colonised by GBS. One case control study supported an association between maternal risk factors and being found to be colonized by GBS in pregnancy and EOGBS in the neonate. A UK HTA considered as part of the previous NSC update report found no association between maternal risk factors and neonatal GBS colonisation. One study from the UK suggested that about two thirds of mothers of EOGBS cases have at least one risk factor. This means that a third of EOGBS cases might be born to women with no known risk factors for GBS, and therefore not targeted with IAP in a risk based approach. This study cannot tell us what proportion of women who do not go on to have babies with EOGBS have risk factors for EOGBS*."

New evidence published since February 2012 is summarised below for each review question individually.

1) Overall incidence of EOGBS in the UK

The search identified six studies investigating the incidence of EOGBS published in the UK since 2012. The results are summarised in **Appendix 13**. In Northern Ireland, a retrospective chart review found that the incidence of EOGBS was 0.57 per 1,000 live births between 2008 and 2010.[46]

Prospective, enhanced, active national surveillance data on invasive GBS infections in infants younger than three months identified 518 cases of EOGBS in the UK and the Republic of Ireland (RoI) over a 13-month period (April 2014 to April 2015 inclusive).[39] The total incidence of EOGBS in all five countries in the British Isles was 0.57 (95% CI: 0.52-0.62) per 1,000 live births. EOGBS incidence was similar across the five countries; the lowest incidence was observed in the RoI (0.45, 95% CI: 0.31-0.63) and the highest incidence in Northern Ireland (0.64, 95% CI 0.38-1.03). The EOGBS incidence in UK and Irish neonates was higher compared to the last national surveillance for GBS conducted in 2000/2001 (0.48, 95% CI: 0.43-0.53 per 1,000 live births) with the biggest increase seen in the Scottish incidence (from 0.21 to 0.49 per 1,000 live births). Subgroup data for England only showed that since the 2000/2001 surveillance, the EOGBS incidence in babies weighing less than 2.5 kg, and less than 1.5 kg, at birth, decreased significantly from 2.13 to 1.34 per 1,000 live births at the indicated weight and from 4.08 to

2.24 per 1,000 live births at the indicated weight, respectively. The rate of early-onset GBS meningitis was 0.062 per 1,000 live births (57 cases per 914,132 live births) in the UK and the RoI over the 13-month period.

National voluntary surveillance data on diagnoses of invasive GBS infection in England and Wales from 1991 to 2010 showed an increase of EOGBS between 1991 and 1997 to a rate of about 0.38 before dropping to a low of 0.28 per 1,000 live births in 2000.[19] Afterwards, a general rise in EOGBS incidence was observed reaching 0.41 per 1,000 births in 2010.

Prospective, national population-based active surveillance on bacterial meningitis in infants aged <90 days in the UK and the Republic of Ireland identified 52 cases of confirmed or possible GBS meningitis in neonates less than seven days over a 13-month period (July 2010 to July 2011).[49] The rate of early-onset GBS meningitis was 0.054 per 1,000 live births (rate calculated by reviewers).

Voluntary surveillance data on streptococcal bacteraemia published by PHE reported 278 cases of early-onset GBS bacteraemia in the UK in 2013[36] and 303 cases in 2014,[37] giving an incidence of 0.38 (95% CI: 0.34-0.43) per 1,000 live births in 2013 and 0.42 (95% CI: 0.38-0.47) per 1,000 live births in 2014.

GBS serotypes in the UK

The search identified two studies[19,39] that investigated serotype distribution of invasive GBS infections in the UK (**Appendix 13**). Enhanced surveillance data from 2014/2015 found that serotype III was the most common serotype in EOGBS cases from the UK and the Republic of Ireland (50.7%), followed by Ia (19.7%), V (7.9%), II (7.5%), Ib (7.0%), and IV (2.6%). The relative distribution from serotype III showed an increase compared to 2000/2001 surveillance data, in which only 38% of all EOGBS cases were associated with serotype III. Multi-locus sequence typing identified 48 sequence types (STs) amongst 229 submitted isolates from EOGBS cases (44% [229/518] submitted for multi-locus sequence typing). ST-17 was the most common sequence type among EOGBS isolates (35.8%; 82/229), followed by ST-23 (16.2%; 37/229); 20 of the STs were novel alleles. The majority of early-onset meningitis cases (62.1%; 18/29) were attributable to ST-17 isolates.

In agreement, voluntary surveillance data, in England and Wales found that serotype III was the most common serotype in EOGBS (41%) between 1995-2010, followed by Ia (26%), V (12%), II (9%), Ib (8%), and IV (1%).[19] Again, serotype III showed a steady increase in relative distribution from 1997-1998 onwards.

2) Risk factors for EOGBS

The search identified two studies from Northern Ireland and from all five countries in the British Isles, respectively, reporting on the distribution of EOGBS by maternal and neonatal factors.[39,46] Preliminary data from the BPSU surveillance study in 2014/2015 included 429 of all 518 EOGBS cases (83%) identified in the UK and the RoI with available clinical information.[39] The most common risk factors were PROM >18 hours in 31.7% (136/429) and preterm labour <37 weeks in 21.9% (94/429). According to current UK risk-based guidelines for prevention, 35.4% (152/429) had one or more RCOG risk factors and 41.3% (177/429) had at least one risk factor based on NICE guidelines (**Table 1**); depending on the risk factors included, there were 41-65% of EOGBS cases whose mothers had no risk factors. When looking at EOGBS cases in term deliveries only (n=335, calculated as 429-94), 63% (212/335) and 67% (225/335) of mothers did not have any RCOG and NICE risk factors, respectively. This decreased to 40% (133/335) if PROM >18 hours was also added to the current UK risk-based strategies. Forty-four percent of those

with RCOG risk factors were treated with IAP, and 12 different antibiotic combinations were used. The median time of IAP administration was two hours prior to delivery (IQR 1-4 hours). Data from England & Wales only showed that the EOGBS incidence was inversely associated with gestational age at birth decreasing from 4.42 per 1,000 live births before 28 weeks of gestation to a rate of 0.41 per 1,000 live births after 37 weeks of gestation (

Table 2).

Table 1. Distribution of EOGBS by maternal risk factors in the UK (question 2)

Study reference	Cases of EOGBS [n (%)]							
	Preterm labour <37 weeks (CDC)	**Intrapartum fever >38°C (RCOG, NICE, CDC)**	**PROM >18 hours (CDC)**	**Known carriage (RCOG, NICE, CDC)**	**GBS bacteriuria (RCOG, NICE, CDC)**	**Other**	**Any**	**None**
BPSU 2016,[39] UK and RoI	94/429 (21.9%)	83/429 (19.3%)	136/429 (31.7%) **In premature deliveries (NICE)** 41/429 (9.6%)	39/429 (9.1%)	18/429 (4.2%)	**Previous baby with GBS disease (RCOG, NICE, CDC)** 2/429 (0.5%) **Preterm pre-labour ROM (NICE)** 49/429 (11.4%)	**NICE:** 177/429 (41.3%) **RCOG:** 152/429 (35.4%) **CDC:** 253/429 (59%)	**NICE:** *252/429 (58%)* Term babies: 225*/335 (67%)* **RCOG:** *277/429 (65%)* Term babies: 212*/335 (63%)* **CDC:** *176/429 (41%)* **NICE, RCOG, or PROM>18 hours** Term babies: *133/335 (40%)*
Eastwood 2014,[46] Northern Ireland	11/43 (25.5%)	*8/43 (18.6%)*	13/43 (30.2%)	*5/43 (11.6%)*	*1/43 (2.3%)*	1/43 (2.3%) Nature of risk factor not identified	24/43 (55.8%)	*19/43 (44.2%)*

BPSU, British Paediatric Surveillance Unit; CDC, Centers for Disease Control and Prevention; EOGBS, early-onset neonatal Group B streptococcal disease; GBS, Group B *Streptococcus*; NICE, National Institute of Health and Care Excellence; NR, not reported; PROM, prolonged rupture of membranes; RCOG, Royal College of Obstetricians and Gynaecologists; RoI, Republic of Ireland; ROM, rupture of membranes.
Numbers in italics were calculated by reviewers.

The study by Eastwood et al. (2014) included 43 cases of EOGBS identified in Northern Ireland between 2008 and 2010. In 55.8% (24/43) of infants with EOGBS, at least one recognised maternal risk factor for GBS was present during pregnancy or labour (Error! Reference source not found.), but 44.2% (19/43) of EOGBS cases did not have any maternal risk factors. In agreement with the data from the BPSU, the most common risk factors were PROM >18 hours in 30.3% (13/43) and preterm labour <37 weeks in 25.5% (11/43). It is important to note that not all of these infants with maternal risk factors would be treated with IAP under the UK risk-based prevention approach, as mothers in pre-term labour and no other risk factors are not treated, and treatment for PROM in term deliveries is not included in the UK guidelines.[13,15]

Table 2. EOGBS incidence in England & Wales in 2014/2015 by gestational age at birth.* (preliminary data by BPSU 2016[39])

Gestation (weeks)	2014/2015	
	Total cases (n)	EOGBS incidence per 1,000 live births (95% CI)
<28	14	4.42 (2.42-7.40)
28-36	68	1.27 (0.99-1.61)
≥37	283	0.41 (0.36-0.46)
All	343	0.46 (0.41-0.51)

* Missing data on gestational age; only 343 of *438 (78.3%)* EOGBS cases in England & Wales included.

3) Clinical presentation of EOGBS in the UK

The search identified two studies reporting on the clinical presentation of EOGBS in Northern Ireland[46] and in all five countries in the British Isles[39]. The surveillance study performed by the BPSU reported that 66.9% of UK and Irish EOGBS cases presented within 24 hours of birth, and only 11.2% presented after 48 hours.[39]

In the study from Northern Ireland,[46] the age at onset of symptoms ranged from less than one hour to six and a half days: 81.4% (35/43) presented on first day of life, the majority (31/35) within 12 hours. Only 9.3% (4/43) presented after 48 hours; three of these infants (75%) presented with positive cerebrospinal fluid (CSF) cultures in addition to positive blood cultures. Clinical signs of sepsis were present in most infants (81.4%) when blood culture was obtained.

4/5) EOGBS mortality rate and its distribution by maternal risk factors in the UK

Four studies were identified that reported data on EOGBS mortality in the UK[38,39,46,51] (see **Appendix *14***).

Preliminary data from UK and Irish EOGBS cases suggest a significant decline in the case fatality rate from 10.6% in 2000/2001 to 5.2% (27/518) in 2014/2015 (p=0.01).[39] Three of 57 (5.3%) babies with early-onset GBS meningitis died. The EOGBS case fatality rate was highest for babies born before 28 weeks of gestation (47.1%; n=8) and was inversely associated with gestational age decreasing to a rate of 2.8% (n=9) in babies born after 37 weeks of gestation (**Table 3**). Prematurity was an independent risk factor for death. Among EOGBS deaths, 37% (n=10) had at least one RCOG risk factor for IAP and 48% (n=13) had at least one NICE risk factor (see **Appendix 15**). Of the 27 EOGBS deaths, only one woman had received IAP in labour. When only looking at EOGBS deaths in babies born after 35 weeks of gestation, there were 70% (7/10) without any RCOG risk factor, 60% (6/10) without any NICE risk factor and 50% (5/10) without any CDC risk factor (which included the additional risk factor of PROM>18 hours compared to the current UK guidelines). In babies born after 37 weeks of gestation, the proportions were similar with 56% (5/9) to 67% (6/9) of EOGBS deaths without any maternal risk factor, depending on risk factors included.

Table 3. Case fatality rate in EOGBS cases by gestational age at birth* (preliminary data from BPSU 2016[39])

Gestation (weeks)	2014/2015	
	Total cases (n)	Case fatality rate (%)
<28	8/*17*	47.1%
28-36	7/*77*	9.1%
≥37	9/*321*	2.8%
All	*24/415*	*5.8%*

* Missing data on gestational age. Only about *415* EOGBS cases (and 24/27 deaths) included.
Number in italics were calculated by reviewers.

Eastwood et al. (2014) reported a direct EOGBS (GBS-positive blood or CSF culture less than seven days) mortality rate of 7% (3/43) in a population of 75,856 live births in Northern Ireland between 2008 and 2010 equivalent to an EOGBS-related death rate of 4.0 per 100,000 live births. Maternal risk factors for GBS were present in all three neonatal deaths.[46]

The study by Williams et al. (2013) evaluated changes in infant deaths from infections, from 1988 to 2008, in the North of England (704,536 live births).[51] Early-onset (symptoms within 48 post-natal hours) GBS-specific neonatal mortality rate was 6.5 per 100,000 live births (95% CI: 4.6-8.4) between 1988 and 2008. This fell significantly from 9.9 (95% CI: 5.7-14.0) in 1995-2001 to 3.6 (95% CI: 1.1-6.1) per 100,000 live births in 2002-2008 ($p<0.002$). Authors indicated this might be due to screening strategies, antibiotic policies, and improvements in neonatal care.

Preliminary data on early GBS-related neonatal deaths (within seven days after birth) as reported to MBRRACE-UK for births in the UK in 2014 identified 17 early GBS-related neonatal deaths (13 with GBS as primary cause of death and four with GBS as co-factor of death) among 777,764 live births corresponding to a rate of 2.2 per 100,000 live births and 1.72% (17/991) of all early neonatal deaths, respectively.[38] Incidence of early GBS-related neonatal death was highest for babies born between 24 and 27 weeks of gestation (203 per 100,000 live births) and was inversely associated with gestational age decreasing to a rate of 0.8 in 100,000 live births after 37 weeks of gestation (**Table *4***). About 65% (11/17) of early onset GBS-related neonatal deaths occurred in preterm babies born before 37 weeks of gestation.

Table 4. GBS-related neonatal deaths within seven days of births by gestational age at birth (preliminary data from Manktelow 2016[38])

Gestation (weeks)	Early neonatal death (per 100,000 live births)
24-27	5/2,463 (203.0)
28-31	1/5,913 (16.9)
32-36	5/48,477 (10.3)
37-41	6/699,114 (0.9)
42+	0/21,797 (0.0)
All	17/777,764 (2.2)

6) Short-term morbidities of EOGBS in the UK

Two studies were identified in this search that reported data on short-term morbidities of EOGBS in England & Wales,[19] and in the UK & the Republic of Ireland[39] (**Appendix 16**). Sepsis was the most frequent short-term morbidity in all five countries in the British Isles in 2014/2015 and was present in 63.1% of all EOGBS cases (range 67% to 100% in premature EOGBS cases and 50% to 69% of term EOGBS cases, depending on country).[39] Pneumonia was present in 23.7% (range: 0% to 33% of premature EOGBS cases and 11% to 50% of term EOGBS cases, depending on country). Six percent of EOGBS cases in England & Wales had a clinical diagnosis of meningitis between 1991 and 2010[19] whereas 13.2% of UK and Irish infants with EOGBS presented with meningitis (range: 0% to 20% depending on country and prematurity) in 2014/2015.

7/8) Long-term morbidities in EOGBS and its association with clinical presentation

The search identified three studies presenting data on EOGBS long-term morbidities[46,50] and/or its association with clinical presentation.[39,50] Results are summarised in **Appendix 17**. The study by Eastwood et al. (2014)[46] reported abnormal neuro-development in 8.7% of surviving EOGBS cases (2/23) at the last paediatric review, while 15 of 38 cases (39%) were lost to follow-up. It was uncertain if these neurological sequelae were directly related to EOGBS infection or were the results of prematurity.

In a Japanese study, 15.8% (12/76) of surviving EOGBS cases had sequelae.[50] A high rate of neurological sequelae was noted among cases with early-onset GBS meningitis (33.3%, 8/24). The morbidity rate was not different between preterm and term neonates.

Preliminary BPSU data[39] from the UK and the RoI in 2014/2015 showed that 25.9% of EOGBS cases presenting with meningitis had a "poor outcome" (definition not reported) and 29.8% had a poor outcome or died. The proportions of EOGBS cases with poor outcomes were lower in babies presenting with sepsis (5.1%) and pneumonia (2.0%).

9/10) Stillbirths associated with GBS in the UK and its association with gestational age

The search identified three studies investigating the rate of GBS-related stillbirths[38,46,52] and/or its association with gestational age.[38,46] Results of a retrospective cohort study,[46] preliminary data reported to MBRRACE-UK[38] and findings from a population-based surveillance study from the North of England[72] included in the systematic review by Nan et al.[52] are reported in **Appendix 18**.

The study by Eastwood et al. (2014) identified five stillbirths related to GBS in Northern Ireland in 2009 (n=3) and 2010 (n=2). Eighty percent (4/5) of these infants were delivered at term. An identifiable risk factor for GBS was present in one mother only (20%) who delivered prematurely and was GBS-positive on vaginal swab. GBS-related stillbirth accounted for 15.6% (5/32) of all stillbirths with infection as definite cause or cofactor of death and 21.7% (5/23) of all stillbirths with infection as definite cause of death. The total number of births in Northern Ireland during these two years and the incidence rate were not reported. By taking live birth and stillbirth data for Northern Ireland in 2009 and 2010 from the Northern Ireland Statistics & Research Agency (NISRA) website[73] (50,225 live births and 224 stillbirths in 2009 and 2010), the rate of GBS-related stillbirths was estimated by the reviewers to be 9.9 per 100,000 total births.

Preliminary data on GBS-related stillbirths as reported to MBRRACE-UK for births in the UK in 2014 identified 31 GBS-related stillbirths (24 with GBS as primary cause of death and seven with GBS as co-factor of death) among 780,979 total births corresponding to a rate of 4.0 per 100,000 total births and

0.96% (31/3,215) of all stillbirths, respectively.[38] Incidence of GBS-related stillbirth was highest for babies born between 24 and 27 weeks of gestation (220 per 100,000 births) and was inversely associated with gestational age decreasing to a rate of 2.1 in 100,000 births after 37 weeks of gestation (

Table 5). About half (16/31) of all GBS-related stillbirths occurred in preterm births before 37 weeks of gestation.

Table 5. GBS-related stillbirth by gestational age at birth (preliminary data from Manktelow 2016[38]) (question 10)

Gestation (weeks)	Proportion GBS-related stillbirth	
	In total cohort (per 100,000 total births)	**Among stillbirth (% stillbirths)**
24-27	7/3,183 (219.9)	7/720 (0.97)
28-31	1/6,449 (15.5)	1/536 (0.19)
32-36	8/49,276 (16.2)	8/799 (1.00)
37-41	15/700,253 (2.1)	15/1,139 (1.32)
42+	0/21,818 (0.0)	0/21 (0.00)
All	31/780,979 (4.0)	31/3,215 (0.96)

A systematic review searching the literature up to March 2015 identified eight studies reporting GBS-related stillbirth rates.[52] The incidence of GBS-related stillbirth varied substantially between studies and ranged from 3.6 to 94 per 100,000 births. One included population-based surveillance study from England[72] reported 23 GBS-related stillbirths (20-42 weeks of gestation) in 631,206 total births between 1981 and 1996, corresponding to the lowest reported incidence of GBS-related stillbirth (3.6 per 100,000 births) among the eight studies. The original study[72] reported 630,206 live births and 3,591 registered stillbirths in the survey area during the study period, which totals to 633,797 births, therefore there may be a discrepancy in the systematic review[52]. Of the 23 GBS-related stillbirths, six occurred at 20-23 weeks of gestation and 17 at 24-42 weeks of gestation. In almost half (46%) of all maternally acquired infectious deaths at 20-23 weeks and 21% of all deaths at 24-42 weeks it was not possible to make a firm microbiological diagnosis and the responsible organism is unknown, so numbers are possibly an underestimation.[72] GBS infection accounted for 0.6% of all stillbirths and 15.8% of all infection-related stillbirths.

11) Maternal GBS carriage rate in the UK

Our search did not identify any new data on the rate of maternal GBS colonisation in the UK since 2012.

12) Variation between antenatal and intrapartum GBS carriage status

Five studies presenting data on the variation between antenatal and intrapartum GBS carriage status were identified in the search (**Appendix 19**).[41,42,44,45,48] Four were prospective cohort studies[41,42,44,45] and one was a retrospective cohort study.[48] All five studies reported that GBS carriage status varied in pregnancy; between 10.9% (5/46)[41] and 32.7% (48/147)[42] of women with positive GBS culture during the

third trimester had a negative GBS culture at term. Between 5.1% (n=69, denominator not reported)[48] and 11.7% (42/360)[42] of women with negative GBS culture during third trimester screening had a positive culture at term.

13/14) Rates of vertical GBS transmission and of resulting EOGBS disease

Our search identified one study investigating the vertical GBS transmission from mother to baby during labour/birth without IAP.[43] Three studies provided data on the proportion of babies with GBS colonisation who become affected by EOGBS disease when not receiving IAP[40,43,47] (**Appendix 19**). Two studies used a prospective cohort design[40,43] and one was a retrospective cohort design.[47] The vertical GBS transmission rate was 57.7% (146/253) for women with positive intrapartum GBS culture not receiving IAP in a prospective study from Gambia.[43]

Berardi et al. (2013) reported one case of early-onset GBS sepsis in 16 colonised neonates (6%) tested within 10-24 hours of birth and 48-72 hours after birth or at nursery discharge and whose mothers did not receive IAP.[40] One study from Gambia[43] reported one case of EOGBS in 186 colonised infants at birth without IAP (0.5%), while a Chinese study including 23 colonised neonates born to GBS carriers with preterm prelabour rupture of membranes (PPROM) <37 weeks of gestation without antibiotic prophylaxis reported six (26.1%) were affected by EOGBS.[47]

15) Bacterial load and bacterial molecular markers predictive of neonatal GBS colonisation or early-onset disease

A summary of the results and the methodological quality of the evidence for each bacterial marker and bacterial load is provided below and in **Appendix 20**. It is important to note that the definition of EOGBS differed across studies. In some it was defined strictly as a positive culture from a normally sterile site, in other studies it was defined as a surface or urine culture being positive in the presence of symptoms. All relative risks or risk ratios (RR) and odds ratios (OR) below are calculated by the reviewers.

Serotypes

The serotypes predictive of GBS transmission from mother to neonate were investigated by Al-Sweih et al. (2005).[53] This study had high risk of bias in study participation and confounding variables. The authors found that mothers colonised with serotypes V (13/27, 48%) and Ia (5/11, 45%) were more likely to transmit GBS than mothers colonised with serotypes Ib (1/3, 33%), III (11/33, 33%), serotypes that were not typeable (7/22, 32%), and the remaining serotypes. However, the calculated relative risk comparing the proportion of serotype V who had EOGBS against EOGBS in all other serotypes was not significant (13/27 [48%] versus 31/97 [32%], RR: 1.51, 95% CI: 0.93-2.45).

The serotypes in asymptomatic GBS colonised neonates were compared to neonates with EOGBS disease in six studies.[54,56,59,68-70] Two studies were at high risk of bias,[54,56] and four studies were at moderate risk of bias for study participation.[59,68-70] Three studies were at high risk of bias,[56,69,70] and three at moderate risk for study confounding.[54,59,68] There was one study at high risk of bias for prognostic factor measurement,[54] and one for outcome measurement as there was no information provided on the definition and measurement of EOGBS or serotyping procedures.[70] In three studies EOGBS was defined as positive culture from a normally sterile site.[56,68,70] However, in Embil et al. (1987) EOGBS included surface cultures,[69] and in Baker et al. (1973) it was “proven septicaemia and/or

meningitis due to GBS".[54] The age of onset also varied between less than three days, equal to or less than five days, less than seven days, and less than 10 days.

Meta-analysis could only be performed on three of these studies comparing occurrence of EOGBS in neonates colonised with different GBS serotypes. Three studies were excluded, as the required data were not available; Baker et al. (1973)[54] counted one participant with EOGBS in both the asymptomatic GBS colonisation group as well as the EOGBS disease group, and the patient's serotype was not reported, Baker et al.'s (1974)[68] findings were confounded by inconsistent reporting of numbers of individuals with GBS sepsis; they variably report 51, 56 and 62 people with GBS sepsis, and Fluegge et al. (2011) only reported the percentage of serotype III in neonates with EOGBS but not other serotypes.[59] Fluegge et al. (2011) reported a higher percentage of serotype III in neonates with EOGBS than in colonised asymptomatic neonates (58% versus 30%, p<0.001).[59] Similarly, Baker et al. (1973) also found that serotype III was more frequently present in EOGBS (7/13 [54%]) than other serotypes (8-20%), and more often than in asymptomatic colonisation (19/54 [35%]). However, Baker et al. (1974)[68] found that infants with asymptomatic GBS colonisation and GBS sepsis were most often type II (38% and 44% respectively), whereas participants with meningitis were most frequently serotype III (80%).

The pooled RRs from the meta-analysis for EOGBS in neonates colonised by comparisons of GBS serotypes are shown in **Figure 2**.

Serotype Ia				
0.96 (0.59 to 1.58)	**Serotype Ib**			
0.76 (0.47 to 1.23)	0.82 (0.47 to 1.44)	**Serotype II**		
1.51 (1.12 to 2.03)	1.48 (0.94 to 2.35)	**1.95 (1.10 to 3.45)**	**Serotype III**	
0.67 (0.26 to 1.72)	0.77 (0.27 to 2.20)	0.82 (0.31 to 2.18)	0.45 (0.19 to 1.10)	**Nontypeable**

Serotype | Pooled association (Risk Ratio [95% Confidence Interval]

Comparisons should be read from right to left. The pooled estimate is located at the intersection of the row-defining serotype and column-defining serotype. A RR value greater 1 means higher risk of early onset GBS in neonates colonised by the row-defining serotype. To obtain RRs for comparisons in the opposing direction, reciprocals should be taken. Significant result is in bold and underlined.

Figure 2. Pooled risk of Early onset GBS by different comparisons of GBS Serotypes colonisation in neonates

Neonates colonised by GBS serotype III had a higher risk of developing EOGBS than neonates colonised by GBS serotype Ia (pooled RR: 1.51, 95% CI: 1.12 to 2.03, three studies, 439 neonates). Such that, among 261 neonates colonised by GBS serotype III, 98 (37.5%) developed EOGBS compared with 45 of 178 (25.3%) colonised by GBS serotype Ia. Similarly, neonates colonised by GBS serotype III were twice as likely to have developed EOGBS than neonates colonised by GBS serotype II (pooled RR: 1.95, 95% CI:

1.10 to 3.45, three studies, 355 neonates). Such that, among 261 neonates colonised by GBS serotype III, 98 (37.5%) developed EOGBS compared with 19 of 94 (20.2%) colonised by GBS serotype II. The results of the meta-analysis showed no evidence of statistically significant differences in the risks of developing EOGBS in neonates colonised by other comparisons of GBS serotype.

Sequence type (ST) and clonal complex (CC)

Fluegge et al. (2011)[59] compared the sequence types and clonal complexes of serotype III strains in asymptomatic neonates colonised with GBS and neonates with EOGBS (blood and CSF culture) disease. This study had no domains at high risk of bias but was at moderate risk of bias for confounding variables, study participation, and attrition. Of the 96 participants with EOGBS, 18 had ST-19, 61 had ST-17, 1 had ST389, and the remaining had other STs, whereas of the 46 participants with asymptomatic colonisation, 0 had ST-19, 11 had ST-17, 22 had ST-389, and the remaining had other STs. The authors reported a significant difference in the numbers of ST-17 and the numbers of ST-389 in invasive versus asymptomatic neonates ($p<0.001$). Regarding clonal complexes, 64/96 (67%) participants with EOGBS were CC-17 and 22/96 (23%) were CC-19, compared to 14/46 (30%) participants with asymptomatic colonisation who were CC-17 and 23/46 (50%) participants who were CC-19.

C-Protein antigen

Chun et al. (1991)[56] investigated whether the C-protein antigen is predictive of EOGBS. This study had high risk of bias in the study participation, and study confounding domain, as well as moderate risk of bias in statistical analysis and reporting. The authors examined whether asymptomatic GBS and EOGBS (blood and CSF culture) strains reacted to C-protein antiserum and four antigens – α, β, γ, δ. They found that 87% (41/47) of neonates with EOGBS and 73% (54/74) of asymptomatic GBS colonised individuals reacted to C-protein antiserum; this difference was not significant. When comparing the distribution of the four C protein-associated antigens, antigen δ was expressed more often in EOGBS neonates (12/41 29%) than in asymptomatic neonates (10/54 19%). The remaining isolates were present less often in EOGBS (α = 28/41 68%, β= 7/41 17%, and γ= 15/41 37% [36.5%]) than in healthy neonates (α = 44/54 81%, β= 15/54 28%, and γ= 20/54 37%). Summary measures were not calculated for the antigens as more than one antigen can be expressed in one neonate. For example, the authors indicated that many neonates who expressed the γ antigen also expressed the α antigen. When the authors compared the distribution of the antigens among septic neonates (EOGBS and LOGBS) to healthy neonates, they did find a significantly higher expression of α in healthy neonates, and of δ in septic neonates. However, multivariate analysis demonstrated that this association was not independent of serotypes.

Bacterial load

There were 12 studies investigating bacterial load[55,57,58,60-67,71]. Eight were on the association of bacterial load from maternal colonisation to neonatal GBS colonisation,[55,58,61,62,64-67] five on maternal colonisation to EOGBS,[55,62,64,65,67] and four on neonatal colonisation to EOGBS.[57,60,63,71] The bacterial load was defined differently across the studies. Four studies investigated the number of positive culture sites,[57,61,63,71] two investigated the number of colonies on a plate,[58,61] one investigated a combination of the number of colonies and positive sites,[60] three investigated GBS colony-forming units,[62,66,67] two investigated the number of hours by which a rapid slice coagglutination test identified GBS,[64,65] and one was based on selective versus standard culture.[55] The definition of EOGBS was strictly culture from normally sterile site in five studies.[60,62,63,67,71]

There was high risk of bias in 10 studies,[55,57,58,60-63,65,66,71] and moderate risk of bias in two studies,[64,67] for confounding variables. In the study participation domain, there were seven studies with high risk of bias,[55,57,58,61-63,71] and five with moderate risk of bias.[60,64-67] Boyer et al. (1983) had high risk of bias in study attrition and outcome measurement,[55] and two studies had high risk of bias in statistical analysis and reporting.[58,61] Only prognostic factor measurement was at low risk of bias across all studies.

Number of sites

Hoogkamp-Korstanje et al (1982)[61] compared the association between one colonised site versus two or more colonised sites in women and the risk of GBS vertical transmission. The sites swabbed were throat, nose, vagina, cervix, rectum, and midstream urine. Women with two or more colonised sites were 2.5 times more likely to have a neonate with GBS than women with only one colonised site (91% versus 36%, RR calculated from percentages given in paper: 2.53, 95% CI: 1.93-3.31).

There were three studies[57,63,71] comparing the association of one to two colonised sites versus three to four colonised sites in neonates and EOGBS. Lin et al. (2006)[63] and Pass et al. (1979)[71] restricted EOGBS to blood and CSF culture, and found a much higher risk of EOGBS in neonates with three to four colonised sites (Lin et al., 2006: 25 per 1,000 versus four per 1,000, p<0.001; Pass et al., 1979: 7/91 [8%] versus 1/199 [0.5%], RR: 15.31, 95% CI: 1.91-122.60). Dillon et al. (1987)[57] included culture from other unspecified clinical specimens in addition to blood and CSF, and also found that EOGBS was more common in neonates with three to four colonised sites compared to one to two sites (20/403 [5%] versus 4/1045 [0.4%], RR: 12.97, 95% CI: 4.46-37.70).

Number of colonies

Two studies[58,61] reported the association between the numbers of colony counts found on a plate and GBS vertical transmission. Easmon et al. (1985)[58] defined four categories of colonisation – greater than 50 colonies on direct plating, 10-50 colonies on direct plating, less than 10 colonies on direct plating or the presence of GBS colonies only on enriched culture medium. The authors reported the bacterial load results separately for rectal and vaginal swabs. However, the labelling of the data in the graph was unclear. Hoogkamp-Korstanje et al. (1982) also found that heavy colonisation (87%) was associated with GBS transmission more often than light (30%) or moderate (50%). Light colonisation was defined as <10, moderate as 10-50, and heavy as greater than 50 colonies all on selective culture.

Gerards et al. (1985)[60] combined the number of sites with the number of colony counts in neonates with asymptomatic GBS colonisation and created the following criteria – light colonisation was fewer than three sites that were <10 or 10-50 colonies, moderate colonisation was fewer than three sites with greater than 50 colonies or three or more sites with <10 or 10-50 colonies, and heavy was three or more sites with greater than 50 colonies per plate. They found that neonates who were colonised with greater than 50 colonies of GBS in three or more sites were more likely to have EOGBS than neonates with less than 50 colonies. Among the eight infants with heavy colonisation: four (50%) had EOGBS; four (50%) had probable sepsis (but no confirmatory culture from a normally sterile site) and zero had asymptomatic colonisation. Among the 35 neonates with moderate colonisation: 15 (42.8%) had EOGBS; 11 (31.4%) had probable sepsis and nine (25.7%) had asymptomatic colonisation. Among the 44 neonates with light colonisation: two (4.5%) had EOGBS; four (9.1%) had probable sepsis and 38 (86.4%) were asymptomatically colonised.

GBS colony forming units

Three studies[62,66,67] investigated the relationship between colony forming units (cfu) and maternal to neonatal colonisation[62,66,67] or EOGBS[62,67]. Sensini et al. (1997) defined light colonisation as 10^2 to 10^6 cfu/GBS ml and heavy colonisation as $\geq 10^6$ cfu/GBS ml, finding that mothers with $\geq 10^6$ cfu/GBS ml were more likely to transmit GBS to their neonates (74/148 [50%] versus 34/112 [30%] RR: 1.65, 95% CI: 1.19-2.28). In this study, only one neonate developed EOGBS and their mother had light colonisation. Persson et al. (1986) investigated cfu/GBS ml in the urine of mothers, similarly finding that those with $\geq 10^4$ cfu/GBS ml were six times more likely to transmit GBS to their neonates compared to mothers with $<10^4$ cfu/GBS ml (6/9 [67%] versus 6/55 [11%] RR: 6.11, 95% CI: 2.52-14.81).

Jones et al. (1994)[62] plotted the cfu/GBS in mothers' vaginas against cfu/GBS in neonates' rectum to obtain a linear regression curve, and found a significant correlation ($p<0.001$). They also found that mothers' swabs had to contain at least 10^2 GBS before the neonate's swab yielded a positive result, and that neonates colonised with $\geq 10^5$ GBS per rectal swab were delivered by mothers colonised with $\geq 3 \times 10^4$ GBS per vaginal swab. The cfu/GBS of mothers' vaginal swabs correlated poorly with neonates' umbilical and nasopharyngeal cultures. Three infants in this study developed EOGBS, two had blood culture positive sepsis and one had rectal culture positive and respiratory distress. All three infants had mothers who were heavily colonised with GBS (7.70×10^6, 6.62×10^7, 2.5×10^6). However, only two of the infants were heavily colonised (7.02×10^5, 5.25×10^6), and one infant with blood culture positive sepsis was lightly colonised ($<10^1$). Authors noted that this infant might have been cleansed before culture.

Other

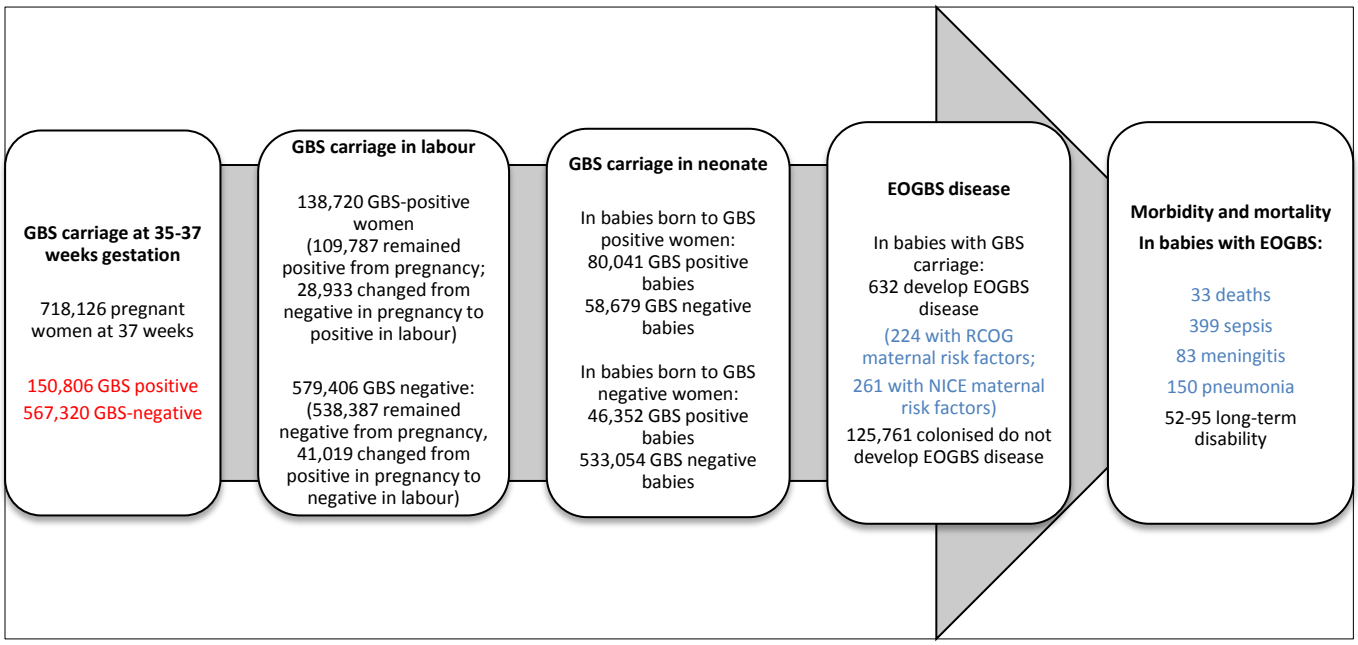
Two studies[64,65] investigated bacterial load in mothers by a rapid slide coagglutination test and categorised colonisation as heavy if agglutination with GBS antigens was detectable within five hours of swab or light if agglutination was negative at five hours but positive at 20 hours. They found that mothers with heavy colonisation who gave birth to term infants were two times more likely to transmit GBS to their neonates than mothers with light colonisation (24/30 [80%] versus 35/98 [36%] RR: 2.24, 95% CI: 1.63- 3.09).[65] Mothers with heavy colonisation who gave birth to pre-term infants were three times more likely to transmit GBS to their neonates than mothers with light colonisation (8/11 [73%] versus 9/37 [24%] RR: 2.99, 95% CI: 1.52-5.87).[64] In 1986, Morales et al. found that the three cases of GBS sepsis (positive body fluid culture) in term births were neonates of mothers with heavy colonisation. In 1987, the group found that GBS sepsis in pre-term neonates (including culture of blood, CSF, urine, and oropharynx cultures with radiographic and clinical signs of infection) was approximately four times more likely in heavily compared to lightly colonised mothers (7/11 [64%] versus 6/37 [16%] RR: 3.92, 95% CI: 1.66-9.25).

Finally, Boyer et al. (1983)[55] categorised the degree of colonisation as:

- Light if intrapartum vaginal culture was negative, but postpartum rectal or vaginal culture was positive;
- Moderate if intrapartum vaginal culture was positive on selective culture only; and
- Heavy if intrapartum vaginal culture was positive on direct plate as well as selective culture.

Here too, neonatal colonisation was 3.29 times more likely in heavy compared to light or moderate colonisation (69/107 [64%] versus 20/102 [20%] RR: 3.29, 95% CI: 2.17- 4.99). Of the women who did transmit GBS to their infants, women with heavy colonisation were more likely to have neonates that were colonised at multiple sites (55%) compared to women with moderate or light colonisation (30%,

p=0.04). The authors found four neonates with EOGBS in their study, all of which had mothers with heavy colonisation.



GBS, Group B *Streptococcus*; EOGBS, early-onset group B *Streptococcus*; NPV, Negative predictive value; PPV, Positive predictive value

a. Term pregnant women available for screening at 35-37 weeks: cohort based on 776,352 live births in the UK in 2014 (Office for National Statistics [ONS], 2015).[74] Of all live births, 7.5% delivered < 37 weeks (applied from England and Wales ONS, 2015)[75] and removed from cohort. Assumes no stillbirth, multiple births, or miscarriages in third trimester.
b. Red: Data from previous review[24]: 21% GBS maternal carriage in the UK
c. Carriage in labour: PPV and NPV from Szymusik et al. (2014)[48] – largest study in current review; study used Center for Disease Control and Prevention (CDC) guidelines at 35-37 weeks and reference standard at time of admission for labour: 72.8% and 94.9% respectively; other figures in this review include between 89.1%, 77.2%, 77.0%, or 71.7% for PPV and 91.2% or 92.2% for NPV; previous review estimates were approximately 60.6%, 70.2% & 87.1% for PPV, and 89.5%, 94% & 95.9% for NPV.
d. GBS colonisation in neonates in this review: 57.7% GBS transmission from women positive for GBS intrapartum; 8.0% from uncolonised women.[43]
e. EOGBS disease based on transition rate from neonatal colonisation to EOGBS disease in this review: five per thousand colonised neonates[43] taken as the most appropriate. If 0.57 per 1,000 live births is applied instead,[39] there are 443 EOGBS cases.
f. Maternal risk factors: 35.4% had at least one RCOG risk factor; 41.3% had at least one risk factor based on NICE guidelines.[39]
g. Mortality in this review: 5.2% taken as most appropriate.[39] If 7% from another study[46] is used, the mortality would be 44 deaths.
h. Short-term morbidity in this review: Meningitis: 13.2%; Sepsis 63.1%; Pneumonia 23.7%[39]
i. Long-term disability in this review: 8.7-15.8% of surviving EOGBS cases.[46,50]
j. If rate is based on incidence of 0.57 per 1,000 live births[39] or 443 cases of EOGBS: 23 deaths, 280 sepsis, 58 meningitis, 105 pneumonia, 37-66 long-term disability.

Figure 3. GBS Natural history

Discussion

Epidemiology

The enhanced active surveillance data reported an incidence for EOGBS of 0.57 per 1,000 live births in all five countries in the British Isles and a case fatality of 5.2%. This, and the other studies included in this review, only included cases of culture-proven EOGBS; therefore the true burden of the disease might be underestimated as the presence of IAP or small blood volume might result in false negative culture. In contrast, analyses of the Hospital Episode Statistics (HES) in England performed by the Royal College of Obstetricians & Gynaecologists (RCOG) found a double to treble rate of EOGBS (1.2 and 1.4 cases per 1,000 live births) between 1 April 2004 and 31 March 2012 when also including suspected but unconfirmed EOGBS cases using ICD-10 codes.[76] However, because this analysis was based on ICD-10 codes from patient records, it is likely an overestimation, as false positive cases that were suspected but unconfirmed, could not be excluded.

The use of voluntary surveillance data in studies might have caused an underestimation of the true incidence of EOGBS due to incomplete reporting. PHE 2014[36] reported about 85% ascertainment for their 2013 data. Lamagni et al. (2014) also suggested a potential underestimation of disease incidence due to fluctuating quality and quantity of surveillance data.[19] The observed rise in EOGBS incidence between 2000 and 2010 might be at least in part due to improved reporting completeness (75% in 2003, rising thereafter to reach 83% in 2010). In the BPSU study, the authors' mention that the observed increase in the EOGBS incidence might be at least in part due to technical improvements in bacterial culturing practices (reducing false negative results), increased awareness of neonatal GBS, or increased case ascertainment in the more recent surveillance. It is also unclear if the observed rise represents a true or clinical difference over time or normal fluctuations by chance. In particular, the two BPSU studies were conducted at two points in time for a one-year period over 14 years apart, which makes it difficult to assess whether the higher incidence rate or the lower mortality rate found in the second period are fluctuations specific to 2014/15 or how these figures may differ across the years. Data on the epidemiology of GBS across time are limiting, as the yearly lab reports are voluntary and do not contain clinical information, while the enhanced surveillance has only been conducted at two distant points in time.

Preliminary BPSU data[39] found that while the overall incidence of EOGBS between the two surveillance periods increased, the EOGBS incidence in premature infants has actually decreased suggesting that clinicians might have particularly targeted IAP efforts towards women in preterm labour. The proportion of EOGBS cases with risk factors common in both surveillance periods decreased for "prematurity" and "prolonged rupture of membranes >18 hours" from 37% to 21.9% and from 44% to 31.7%, respectively, and increased for the risk factor "known GBS carriage" from 4% to 9.1%. Notably, prematurity per se and PROM in term births are not considered risk factors indicating IAP by the RCOG and NICE. More than half of UK and Irish mothers with EOGBS babies did not have any RCOG or NICE risk factors and therefore no indication for IAP. Preliminary BPSU data suggest that 44% of women with at least one RCOG risk factor had received IAP; duration of IAP was less than two hours in half of these women and only 25% received IAP of at least four hours prior to delivery. Among EOGBS cases born at term, which the review authors calculated as 335 (429 minus 94 preterm births), 63% (212/335) and 67% (225/335) did not have any RCOG and NICE maternal risk factors, respectively. This is the cohort that universal screening would try to detect. A risk-based prevention strategy including PROM >18 hours as risk factors would miss 40% (133/335) of term EOGBS cases.

It is unclear how representative the reported data on GBS serotype distribution and sequence types in the BPSU study are, as only 44% (229/518) of GBS isolates were submitted for serotyping and multi-

locus sequencing.[39] In the study by Lamagni et al. (2014) only 55% of GBS isolates were submitted for serotyping in infant cases with invasive GBS disease (less than 90 days).[19] No separate data on the completeness of isolate submissions for early-onset cases was provided in this study.

Although the incidence rate of EOGBS in the UK and the Republic of Ireland has increased from 2000/2001 to 2014/2015, the EOGBS case fatality rate between the two surveillance periods has halved. Of all EOGBS deaths with information on gestational age at birth (24/27), 42% (n=10) were infants born after 35 weeks. Seventy percent (7/10) of them had no RCOG risk factors, and 60% (6/10) had no NICE risk factors; It is the death in these babies which universal screening would try to prevent. A risk-based prevention strategy including PROM >18 hours as risk factors would miss 50% (5/10) of term EOGBS deaths. Findings of EOGBS-related mortality rates may represent the minimum contributions, as causal pathogens may not always be identified. Retrospective data collection relies on the thoroughness of the clinical and pathology teams at the time, and again, data from voluntary surveillance studies may be influenced by the completeness and quality of surveillance data with a potential underestimation of the number of deaths caused by EOGBS.

The same limitations must be acknowledged for the reported GBS-related stillbirth data. Confidence in these data depends on the completeness of pathological and microbiological assessment of stillbirths and placentas. Eastwood et al. (2014) reported that in Northern Ireland, approximately 55% of stillbirths undergo post-mortem examination.[46] The UK study by Embleton et al. (2001)[72] found that in almost half (46%) of all maternally acquired infectious deaths at 20-23 weeks and in 21% of all maternally acquired infectious deaths at 24-42 weeks it was not possible to make a firm microbiological diagnosis and the responsible organism was unknown, so GBS as cause of pre-delivery death is possibly underestimated. As intrauterine death preceded labour in this study, the administration of IAP was not possible and antenatal screening for GBS carriage would not have prevented these deaths. Preliminary stillbirth data for births in 2014 reported by MBRRACE-UK[38] are almost identical to the results from the UK study from 1981-1996[72] included in a recent systematic review[52]. The results from other (non-UK) studies in this review reported higher GBS-related stillbirth rates. Confidence in the preliminary MBRRACE-UK data depends on the completeness of reporting. The gestational age breakdown indicated that about half of the deaths were at ages before antenatal culture screening results would be available (<37 weeks). The systematic review by Nan et al. (2015)[52] concluded that the epidemiological evidence on GBS-related stillbirth is sparse and stillbirth definition and diagnostic methods were not consistent among the studies. No clear pattern was observed in this systematic review regarding the timing of GBS-related stillbirths. Timing of stillbirth was only reported in two non-UK studies suggesting that approximately 50% of GBS-related stillbirths were reported at 20-28 weeks of gestation, and 50% after 28 weeks of gestation. The authors remarked that this observation might be biased by differences in stillbirth definitions. The impact that antenatal culture screening at 35-37 weeks' gestation and providing IAP to screen-positive women would have on GBS-related stillbirths is therefore unclear.

N**atural history**

The natural history of GBS is summarised in **Figure 3** on a hypothetical cohort of 780,000 pregnant women. The 2016 review search did not identify any new data on the rate of maternal GBS colonisation in the UK since 2012.

Five studies consistently reported that GBS carriage status varied in pregnancy and that between 10.9% (5/46)[41] and 32.7% (48/147)[42] of women with positive GBS culture during the third trimester had a negative GBS culture at term while 5.1% (numbers not reported)[48] to 11.7% (42/360)[42] with a negative GBS culture during the third trimester had a positive GBS culture at term. Differences in the rates might

be explained by the time interval between the third trimester and intrapartum tests, the sensitivity and specificity of the employed enriched culture method, or the colonising GBS serotype. Kwatra et al. (2014) reported that serotype III was more likely to be associated with persistent colonisation between 20-37+ weeks' gestation (29%) than Ia (18%; p = 0.045) or V (6%; p = 0.002).[42]

The vertical transmission rate in women with GBS carriage who were not treated with IAP was assessed in one study only. The study was conducted in Gambia and therefore findings may not be applicable to the UK, due to possible differences in GBS colonising serotypes or delivery and labour care, for example. As many countries now recommend administration of IAP for mothers known to carry GBS, evidence on the natural history of GBS in women and babies without antibiotic prophylaxis is rare and mostly restricted to women in whom precipitous labour, unknown GBS carrier status at delivery, or non-adherence to the management protocol led to non-administration of IAP.

All studies consistently showed an association between women carrying a heavier bacterial load of GBS (all definitions) and neonatal colonisation. Women colonised with a heavy GBS load (>1 site, >50 colonies, or $>10^6$ cfu/ml, quicker identification on rapid test) had approximately two to three times higher risk of having a neonate with GBS colonisation compared to mothers with light GBS load.[58,61,64,65] Women with $>10^4$ cfu/GBS ml on urine culture were six times more likely to have a neonate with GBS colonisation than those with lower bacterial loads.[66] Colonisation status categorised as the presence of GBS colonisation on standard versus selective culture also showed a higher risk with heavy colonisation.[55]

Evidence on the relationship between the bacterial load in the mother and the risk of EOGBS disease was less clear as some neonates with EOGBS had mothers with light colonisation whereas others had heavy colonisation. Reviewers could only calculate these differences statistically from Morales et al. (1987),[64] where EOGBS was almost four times more likely in infants with heavily colonised mothers. However, the definition of EOGBS was not restricted to sterile site culture and the methods of assessing bacterial load were non-standard.

On the other hand, heavier GBS load in neonates (all definitions) was also consistently associated with EOGBS. Neonates colonised with three to four sites were up to 15 times more likely to have EOGBS than neonates colonised with one to two sites [57,63,71]. Similarly, colonised neonates with greater than 50 colonies in three sites were more likely to have EOGBS than those with fewer than 50 colonies and/or sites[60].

There is little evidence on the association between bacterial markers with GBS transmission or transition. The pooled comparison of serotypes in GBS colonised neonates showed a trend towards serotype III being more associated with EOGBS than all of the other serotypes. EOGBS was 1.5 times higher in serotype III than in serotype Ia and almost two times higher than serotype II.

The risk of bias across the studies investigating the bacterial load and bacterial molecular markers was high or moderate in the confounding variables and study participation domain and there was no study that was at low risk of bias for all of the domains. Furthermore, most of the statistical analyses were calculated by the reviewers and therefore unadjusted. There is a risk that these relationships between bacterial load or serotype and neonatal GBS colonisation or EOGBS disease is uncertain and could be partially or entirely due to confounding factors. The applicability of the findings may also be questioned as majority of the studies are quite old (before the 1990s), and might not be applicable to the UK context today. For example, the distribution of bacterial markers may have changed, and standardisation of microbiological testing may be more robust compared to the study settings.

The proportion of colonised neonates affected by EOGBS disease varied from 0.5% (1/186) in a study from Gambia to 26% (6/23) in a study performed at a Chinese hospital. The Gambian study[43] noted that several infants died of early onset pneumonia without a culture-positive diagnosis and the burden of EOGBS disease might have been underestimated. Participants in the Chinese study were GBS-positive women with PROM before 37 weeks;[47] colonised babies of mothers who are GBS carriers and have risk factors (PROM, preterm delivery) might have a higher risk of being affected by EOGBS disease. In addition, the number of colonised babies born to untreated, carrier women was small in all three studies and ranged from 16 to 186. Therefore, the confidence in the estimates is reduced.

Summary

Criterion 1: Not met

The previous review[24] reported that the evidence on EOGBS being an important condition was met as it was still the leading cause of sepsis with an incidence of 0.41 per 1,000 live births and 10% case fatality. EOGBS disease remains an important health problem. According to the most recent enhanced surveillance data available from the BPSU, the overall incidence of EOGBS in the UK and Republic of Ireland was 0.57 per 1,000 live births over 13 months from April 2014. While the overall incidence of EOGBS has increased, the case fatality rate has halved to 5.2% in UK and Irish EOGBS cases in 2014/2015 compared to the 2000/20001 surveillance. The GBS-related stillbirth rate was 4.0 per 100,000 total births in the UK in 2014; about half of the stillbirths occurred before 37 weeks of gestation. Approximately 1% of all stillbirths in the UK were caused mainly or partly by GBS.

The previous review reported that the natural history and epidemiology of GBS is only partly understood and therefore the criterion was only partly met. Partly met is no longer a classification used by the UK NSC. The evidence in this update review consistently reported that GBS carriage status varied in pregnancy and up to 33% of women with positive GBS-culture during third trimester were GBS-negative at term (overtreatment), while up to 12% changed from GBS-negative to positive and would miss out on IAP. There was no evidence that could reliably predict which women would change from GBS positive to negative or vice versa. No new evidence concerning the maternal GBS carriage rate during third trimester in the UK was identified. Vertical transmission rate of GBS-carrier mothers in labour not receiving IAP to the baby was 58% in the only identified study from Gambia. Findings on the proportion of GBS colonised babies who are affected by invasive EOGBS without IAP treatment were not consistent (possibly due to small sample sizes and/or differences in the maternal risk factors) and varied between 0.5% and 26%. It remains only partly understood which GBS-positive mothers at birth transmit the bacterium to their neonate and in which GBS colonised neonates colonisation does result in EOGBS disease. There was evidence that heavier bacterial load in mothers and in neonates increases the risk of GBS transmission and/or EOGBS, and that serotype III in neonates is associated with a higher risk of EOGBS. However, the evidence for these relationships is old, unadjusted, and at high to moderate risk of bias.

Overall, criterion 1 is not met based on the evidence from this review, as we cannot reliably predict which women will change their GBS carriage status between third trimester and birth, or which mothers will transmit GBS to their neonates, or which of these colonised neonates go on to develop GBS disease.

4.3 Evidence on the UK NSC criterion addressing the test (key question 16 and 17)

16. What is the sensitivity and specificity of selective antenatal culture screening tests?
17. What is the predictive value of selective antenatal culture screening tests for a) carriage status at term and b) EOGBS disease?

These questions relate to UK NSC criterion 4:

"There should be a simple, safe, precise and validated screening test."

In GBS screening studies, the same test is being carried out at two different time points when colonisation status may not be the same (35-37 weeks compared to intrapartum), with no other reference standard performed. Inconsistencies in test results between the two time points could possible be due to true transition over time or are a result of test errors at antenatal screening or in labour. These studies are therefore not strictly test accuracy studies, we are interested in the ability of the test to predict future colonisation status, and future development of EOGBS. Below is an explanation what the terms sensitivity, specificity, positive and negative predictive value refer to in this update report when they are applied to studies comparing test results from the same test performed at two different time points. However, it should be noted that because of these definitions due to the difference in time, it is not possible to know the true sensitivity and specificity.

- *False negatives*: Women who screened negative at 35-37 weeks of gestation but who were positive at the time of labour, as determined by selective culture testing.
- *False positives*: Women who screened positive at 35-37 weeks of gestation but who were negative at the time of labour, as determined by selective culture testing.
- *Sensitivity*: Proportion of women with a positive culture screening test at time of labour who were also culture positive at 35-37 weeks of gestation.
- *Specificity*: Proportion of women with a negative culture screening test at time of labour who were also culture negative at 35-37 weeks of gestation.
- *Positive predictive value (PPV) for intrapartum GBS carriage*: Proportion of women who screen positive for GBS at 35-37 weeks of gestation and remain positive at the time of labour, as determined by selective culture testing.
- *PPV for EOGBS disease*: Proportion of women who screen positive for GBS at 35-37 weeks of gestation based on selective culture testing that have a baby with EOGBS.
- *Negative predictive value (NPV) for intrapartum GBS carriage*: Proportion of women who screen negative for GBS at 35-37 weeks of gestation that remain negative at the time of labour, as determined by selective culture testing.
- *NPV for EOGBS disease*: Proportion of women who screen negative for GBS at 35-37 weeks of gestation whose baby is not affected by EOGBS disease.

Description of the evidence

Six studies that addressed the test accuracy questions related to NSC criterion 4 were included (see **Appendix 6**). Included studies are summarised in **Appendix 21**. All six studies were cohort studies; data were collected prospectively in five studies[40,41,44,45,77] and retrospectively in one study.[48] The number of

women included in the analysis of antenatal culture GBS screening test performance ranged from 53[77] to 289[41] in five studies and was unclear in one study.[48] Four studies investigated the predictive value of an antenatal culture screening test performed between 35-37 weeks for intrapartum GBS carriage[41,44,45,48], while two studies presented data which allowed an estimation of the predictive value of antenatal culture screening at 35-37 weeks for neonatal EOGBS disease in a statistical analysis performed by the reviewers.[40,77]

Timing of the screening test was at 35-37 weeks in five studies[40,44,45,48,77] and 35-37 weeks or less than or equal to five weeks prior to delivery in one study.[41] The swab site was recto-vaginal in four studies[40,41,45,77] and not reported in two studies.[44,48] Selective culture medium was used in two studies[40,41] and was not reported in the remaining four studies.[44,45,48,77] Three studies[45,48,77] with unclear reporting on swab site and/or culture medium were included in this update review as the studies referred to the revised CDC guidelines from 2002[78] or 2010[14] which recommend recto-vaginal swabs and the use of selective culture. The study by Mackay et al. (2012) was performed in the USA and the reviewers only presumed that the CDC guidelines were adhered to.

Methodological quality of included studies

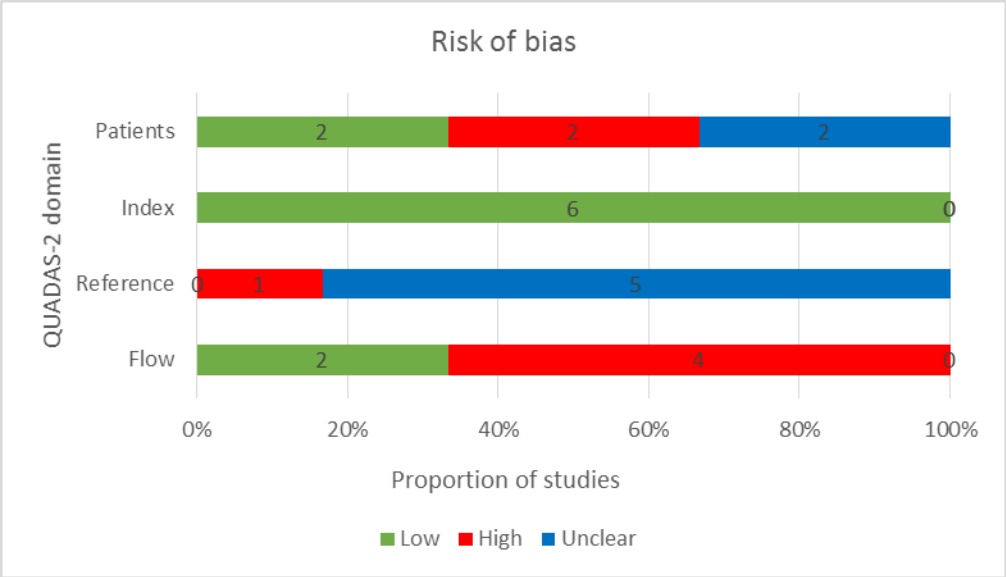
The methodological quality of the six included studies, assessed by untailored QUADAS-2[27] is summarised in **Risk of** bias judgements: Low= The study methods for the respective domain are unlikely to have introduced bias; High= The study methods in the respective domain are likely to have introduced bias; Unclear= It is uncertain if the study methods in the respective domain could have introduced bias.

Figure 4,

Applicability judgements: Low= There are low concerns that population, index test and reference standard, respectively, do not match the review question; High= There are high concerns that population, index test and reference standard, respectively, do not match the review question; Unclear: It is uncertain whether population, index test and reference standard, respectively, match the review question.

Figure 5 and **Appendix 28**. Risk of bias was considered high in two or more domains in three of six studies[40,41,77] (50%) and in one domain in one study[48] (17%). Two studies[44,45] (33%) received no high risk of bias rating but were still judged as unclear risk of bias in one and two domains, respectively. **Risk of** bias judgements: Low= The study methods for the respective domain are unlikely to have introduced bias; High= The study methods in the respective domain are likely to have introduced bias; Unclear= It is uncertain if the study methods in the respective domain could have introduced bias.

Figure 4 shows that study flow was the area with the greatest risk of bias (4/6, 67% high risk). Another issue was incomplete or unclear reporting, particularly of the conduct of the reference standard, which is reflected in high proportions (five [83%] of six studies) scoring an unclear risk of bias in this domain. High risk of verification bias was present in one study looking at predictive value for EOGBS disease[77] as the results of the antenatal GBS screening were known to the clinicians and babies "at risk" were monitored more closely than babies born to GBS-negative mothers.



Risk of bias judgements: Low= The study methods for the respective domain are unlikely to have introduced bias; High= The study methods in the respective domain are likely to have introduced bias; Unclear= It is uncertain if the study methods in the respective domain could have introduced bias.

Figure 4. Risk of bias in six included studies according to unadjusted QUADAS-2[27]

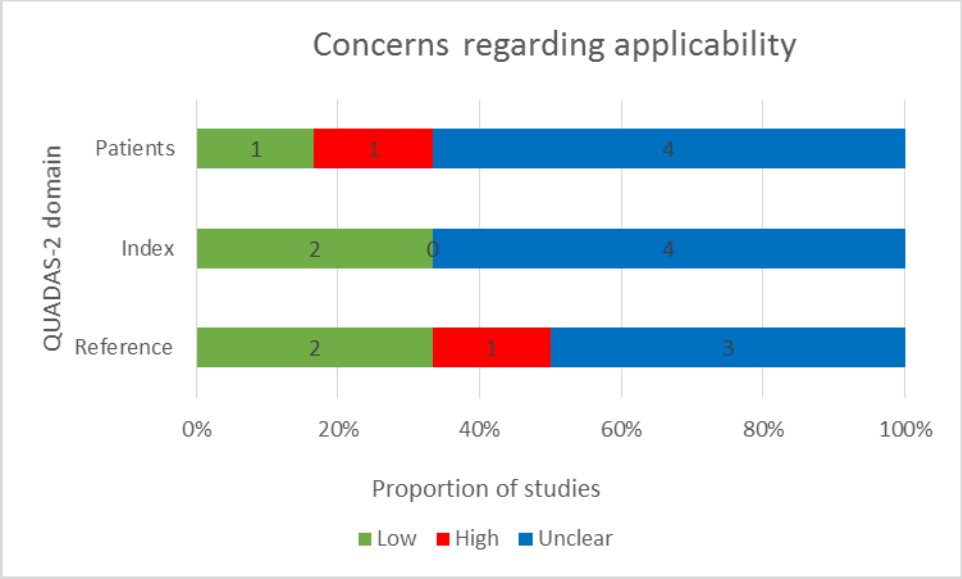
Concerns regarding applicability of the research identified to the UK screening population were unclear or high in five out of the six (83%) included studies (see

Applicability judgements: Low= There are low concerns that population, index test and reference standard, respectively, do not match the review question; High= There are high concerns that population, index test and reference standard, respectively, do not match the review question; Unclear: It is uncertain whether population, index test and reference standard, respectively, match the review question.

Figure 5). This is because no information was given about the ethnicity of the study participants in four studies (unclear concerns)[40,41,48,77], while in one study, the ethnicity was different from the UK with only 52% Caucasian but 23% African-American women included (high concerns).[44] Incidence of EOGBS is reported to be higher in certain ethnic groups (i.e. African-Americans), which might influence the predictive values of the screening test.

Concerns regarding the applicability of the index test to the situation in the UK were classified as unclear in four studies as swab site[44,48] and/or the culture medium used[44,45,48,77] were not reported.

Concerns regarding the applicability of the reference standard for intrapartum GBS carriage to our review question were classified as unclear[48] or high[41] in two studies as it was performed not only in labour but up to seven days prior to delivery[41] or swab site and culture medium were not reported.[48] The reference standard for EOGBS presence or absence was unclear in both studies included for this review question as the diagnostic methods for EOGBS were not reported[40] or included GBS positive urine culture (urinary tract infections).[77]



Applicability judgements: Low= There are low concerns that population, index test and reference standard, respectively, do not match the review question; High= There are high concerns that population, index test and reference standard, respectively, do not match the review question; Unclear: It is uncertain whether population, index test and reference standard, respectively, match the review question.

Figure 5. Applicability concerns in six included studies according to QUADAS-2[27]

Analysis of the evidence

The previous review[24] concluded that, "*antenatal culture results do not perfectly predict culture results for swabs taken at the time of labour and delivery, in part because colonisation status is thought to vary. The studies identified focused on the performance of antenatal culture for predicting intrapartum GBS colonisation, rather than for predicting EOGBS. One systematic review found that on average about 70% of women who test positive for GBS on antenatal screening after 35 weeks of pregnancy also test positive during labour, while on average about 95% of women who test negative on antenatal screening after 35 weeks of pregnancy also test negative during labour. The largest subsequent study (n=5,497) looking at the same aspect of performance of the test in routine clinical practice in the US found that 50.5% of women who tested positive for GBS on antenatal screening also tested positive during labour, while 91.7% of women who tested negative on antenatal screening also tested negative during labour. This means that 49.5% of the women testing positive on screening would be treated with IAP despite not being GBS positive at the time of labour (overtreatment). Also, 8.3% of women testing negative on screening would not be treated with IAP despite being GBS positive at the time of labour (undertreatment). Looking at only the women who were screened at the recommended time [(35 to 37 weeks], 60.6% of women who tested positive for GBS on antenatal screening also tested positive during labour, while 89.5% of women who tested negative on antenatal screening also tested negative during labour.*"

Results from this review are reported in **Appendix 22** and **Appendix 23**. Consistent with the previous review, the PPV of antenatal culture screening performed at 35-37 weeks to predict intrapartum GBS carriage ranged from 71.7% to 77.2% in the four of the six included studies where PPV was reported or could be calculated.[41,44,45,48] One study[41] reported that the PPV improved from 77.2% to 89.1% when

only women with recto-vaginal swabs and selective culture medium were included in the analysis. The NPV of antenatal culture screening performed at 35-37 weeks for intrapartum GBS carriage was 92.2% and 94.9%, respectively, in the two studies assessing this outcome.[41,48] The NPV did not improve by only including women with recto-vaginal swabs and selective culture medium.[41]

The proportion of women with positive GBS culture during labour who were also positive at 35-37 weeks was 71.0%[41] and 76.1%[48], respectively, and improved to 83.7% when only women with recto-vaginal swabs and selective culture medium were included in the analysis.[41] The proportion of women with negative GBS culture at the time of labour who were also negative at 35-37 weeks was 94.3%[41] and 94.0%[48], respectively.

Two studies reported data that allowed an estimation of the value of antenatal culture screening for predicting EOGBS in neonates (**Appendix 23**). From two Italian cohort studies, 4.2% (1/24) and 5.7% (3/53) of women with positive antenatal GBS culture at 35-37 weeks of gestation and no IAP had a baby with EOGBS.[40,77] However, this is very high compared to the findings of EOGBS incidence rates in the UK, which may be due to the small number of participants in the studies. The lower end of the 95% CI was 0.4% and 0.6%, respectively. No women with negative antenatal GBS culture and without IAP had a baby with EOGBS (NPV 100%).[40]

Routine UK data suggests that the PPV of testing pregnant women for GBS colonisation in the third trimester to predict EOGBS disease development in the baby may be only around 0.2%. The BPSU study shows that there are around 350 EOGBS babies born at term in the UK over the course of a year (485 EOGBS in the UK; 78.1% term = 379 / 13 months = 29.2 x 12 months = 350). ONS data shows that there were in total 776,352 babies born per year in the UK (Office for National Statistics, 2015),[74] of which approximately 718,126 were term (≥37 weeks, estimated from applying figures from England and Wales)[75]. Maternal colonisation from the previous UK NSC review is estimated at 21%, equivalent to approximately 150,806 pregnant women who would be colonised with GBS in the third trimester. Therefore, even a test assumed to be perfect at detecting maternal colonisation in the third trimester of pregnancy, would have a PPV of just 0.2% (350/150,806) for detecting EOGBS in the newborn child.

This can be calculated in a different way, by combining studies which estimate each point in the natural history pathway. In 150,806 women colonised in the third trimester, only 333 would go on to develop EOGBS. So again for a test which may be perfect at detecting GBS colonisation of the mother in the third trimester, it would only achieve a PPV of 0.2% as a test to predict having a baby which develops EOGBS. This figure does contain large uncertainties due to the uncertainty present in the estimate for each point in the pathway.

Discussion

Study evidence

Four studies comparing GBS carriage status as determined by selective culture screening performed at 35-37 weeks and intrapartum were identified. A further two studies reported data on the predictive value of selective culture screening at 35-37 weeks of gestation for EOGBS disease. Five were prospective cohort studies and one was a retrospective cohort study. The number of women included in the analysis of antenatal culture GBS screening test performance ranged from 53[77] to 289[41] in five studies and was unclear in one study.[48]

Risk of bias

Risk of bias was considered high in two or more domains in three of six studies (50%) and in one domain in one study (17%). Two studies (33%) received no high risk of bias rating but were still judged as unclear risk of bias in one and two domains, respectively. One of the two included studies that reported number of EOGBS cases in women with positive GBS culture at 35-37 weeks did not describe the definition of presence or absence of EOGBS. The other study had a high risk of verification bias as the results of the antenatal GBS screening were known to the clinicians and babies "at risk" were monitored more closely than babies born to GBS-negative mothers.

Applicability

The screening population itself (i.e. general obstetric population) was directly applicable to a UK screening programme in only one of six included studies. In four studies, no information was given about the ethnicity of pregnant women while in one study, the ethnicity was different from the UK with 52% Caucasian and 23% African-American women included. Incidence of EOGBS is higher in babies of Black women and Black race was identified as independent risk factor for EOGBS;[14,79] predictive values of the screening test might therefore be affected by ethnicity.

Concerns regarding the applicability of the index test to a UK screening programme were classified as unclear in four of six studies (67%) as swab site and/or the culture medium used were not reported.

Concerns regarding the applicability of the reference standard for intrapartum GBS carriage to a UK screening programme were classified as high in one of the four included studies as it was performed not only in labour but up to seven days prior to delivery and was unclear in another study as swab site and culture medium used were not reported. The reference standard for EOGBS presence or absence was unclear in both studies included for this review question as the diagnostic methods for EOGBS were not reported or included GBS positive urine culture (urinary tract infections).

Consistency

Results from the four cohort studies investigating the performance of antenatal culture screening at 35-37 weeks of gestation compared to selective culture testing during labour were consistent. Data taken from two Italian prospective cohort studies with another focus consistently reported that 4% (1/24) to 6% (3/53) of women who screened positive for GBS at 35-37 weeks and did not receive IAP had a baby affected by EOGBS, but results are not definite as only a small number of women were included in this analysis and 95% confidence intervals that the reviewers calculated were wide (0.6-12.8%[40] and 0.4-40.0%[77]). The figures are also not consistent with figures reported for EOGBS incidence in the UK, and likely to be much lower. Using a combination of studies that estimate each point in the natural history pathway, and using the number of cases found in the BPSU study against population figures, indicates that due to changes in colonisation over time, incomplete transmission to the baby, and GBS colonisation infrequently progressing to EOGBS the PPV for third trimester culture to predict EOGBS in the baby may be approximately 0.2%. Each of these estimates come with the uncertainties noted above, however, the estimate of 0.2% is preferred as these are derived from larger numbers. None of 52 women who screened negative for GBS at 35-37 weeks of gestation and did not receive IAP had a baby with EOGBS. Again, the number of included women for this analysis was small and the lower limit of the 95% CI for the NPV was 96.6%.

This report did not assess the test accuracy of rapid tests for detection of maternal GBS colonisation during labour. This area may need further investigation, as one key problem with selective culture screening at 35-37 weeks' gestation is the change of maternal GBS colonisation status between screening and birth. Research on the accuracy of rapid PCR tests in the UK is on-going (GBS2 study; http://www.nets.nihr.ac.uk/projects/hta/138204) and results are to be published in May 2019. Rapid PCR is the most promising of the current tests in labour, however, PCR comes with its own limitations. It is unable to provide information on antibiotic susceptibility, technical expertise is required for administration, and women would be required to arrive in time for the test and IAP. Furthermore, even with intrapartum tests, a large proportion of women colonised with GBS in labour will not transmit the bacterium to their neonate or have a baby with EOGBS, so a substantial amount of overtreatment may still occur.

Summary

Criterion 4: Not met

The previous review[24] reported that the criterion of a precise and validated test was not met as the evidence shows that the GBS carriage status at 35-37 weeks gestation is not a good predictor of GBS carriage in labour, GBS transmission to neonates, or EOGBS disease. The evidence analysed in this review is consistent with the previous judgement as up to 28% of screen-positive women with antenatal culture screening at 35-37 weeks gestation would test negative at birth and may be overtreated, and up to 9% of screen-negative women at 35-37 weeks gestation would test positive at birth and may be undertreated. It is unclear if discordance between GBS culture test results from the third trimester and in labour are a result of test errors giving incorrect results at that time, or because of genuine changes in the status of maternal GBS colonisation over time. Test accuracy of culture cannot be reliably measured because it is the best available test and therefore the reference standard. PPV of antenatal culture screening for EOGBS was not assessed in the four included test accuracy studies. Two small studies with another focus revealed 95% CI estimates for EOGBS disease ranging from 0.4-40.0% and 0.6-12.8%, but the definition of presence or absence of EOGBS was unclear in one study and included UTIs in the other. There is a high degree of uncertainty around this figure because of the small number of participants in the studies. PPV estimates based on larger numbers from this review are approximately 0.2%. A high proportion of women who do remain positive at birth would also be overtreated, as they do not transmit GBS to their neonates or have babies with EOGBS disease. Taken together, enriched culture at 35-37 weeks of gestation is not an accurate predictor of colonisation status at labour, GBS transmission or EOGBS disease in the baby. Screening at 35-37 weeks also misses preterm births, which are at higher risk of EOGBS infection. Therefore, as an indication for IAP, the value of enriched culture at 35-37 weeks of gestation is limited.

4.4 Evidence on the UK NSC criterion addressing the treatment (key question 18 - 20)

18. What is the reported effectiveness of IAP in preventing EOGBS related morbidity and mortality in screen-detected populations?
19. What is the reported effectiveness of IAP in preventing culture negative/probable EOGBS in screen-detected populations?
20. What adverse events do women or children experience after receiving IAP treatment for any prophylactic reason?

These questions relate to UK NSC criterion 9:

"There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care."

Description of the evidence

The effectiveness of IAP treatment questions related to criterion nine were addressed in eight studies (see **Appendix 6**), which are summarised in **Appendix 24** and **Appendix 25**. Five studies were cohort studies; three of them were prospective[40,77,80] and two were retrospective.[81,82] Among the remaining three studies was one uncontrolled before-after study with retrospective data collection,[83] one secondary analysis of a multistate cohort with propensity score matching[84] and one systematic review.[85] A statistical analysis was performed by the reviewers in five[40,77,80,81,83] of the seven included observational studies that had another focus but provided data on the number of EOGBS cases in GBS-positive women who received or did not receive IAP.

Three studies[40,83,84] compared IAP treatment with no IAP. Another three studies[77,80,81] compared IAP ≥4 hours prior to delivery with IAP <4 hours or no IAP. One study[82] compared the effects of IAP ≥4 hours versus IAP <4 hours only. The systematic review[85] included four studies involving 852 women; three studies compared penicillin or ampicillin intrapartum prophylaxis with no IAP, and one study compared ampicillin versus penicillin. The number of women included in the analysis in the seven observational studies ranged from 74[40] to 4,782.[82] Eight studies reported the effect of IAP on culture-proven EOGBS (question 18)[40,77,80-85] and three studies on probable/culture-negative EOGBS (question 19).[81,83,85]

The systematic review on the adverse events from IAP (question 20) resulted in inclusion of 26 studies (**Appendix 26** and **Appendix 27**).[63,86-110] Twelve were cohort studies,[63,86-88,90-92,94,97-100] three were case control studies,[89,93,108] and 11 were randomised controlled trials (RCTs).[95,96,101-107,109,110] Seven studies compared IAP specifically for GBS prevention,[86,89-91,94,100,108] two included IAP for GBS prophylaxis as well as other indications,[92,97] three were for post-partum infection prevention,[95,103,104] eight were for preterm labour,[96,101,102,105-107,109,110] and in six studies the indication for prophylaxis was not stated.[63,87,88,93,98,99] However, as all participants in Lin et al. (2006)[63] were infants colonised with GBS who were actively surveyed at the time of birth, prophylaxis was most likely for GBS.

Many of the controlled trials did not explicitly investigate the adverse events of IAP but reported side effects in their write up. In addition to the side effects, these trials investigated outcomes such as neonatal infection, maternal infection, and hospitalisation, caused by preterm labour or infection in

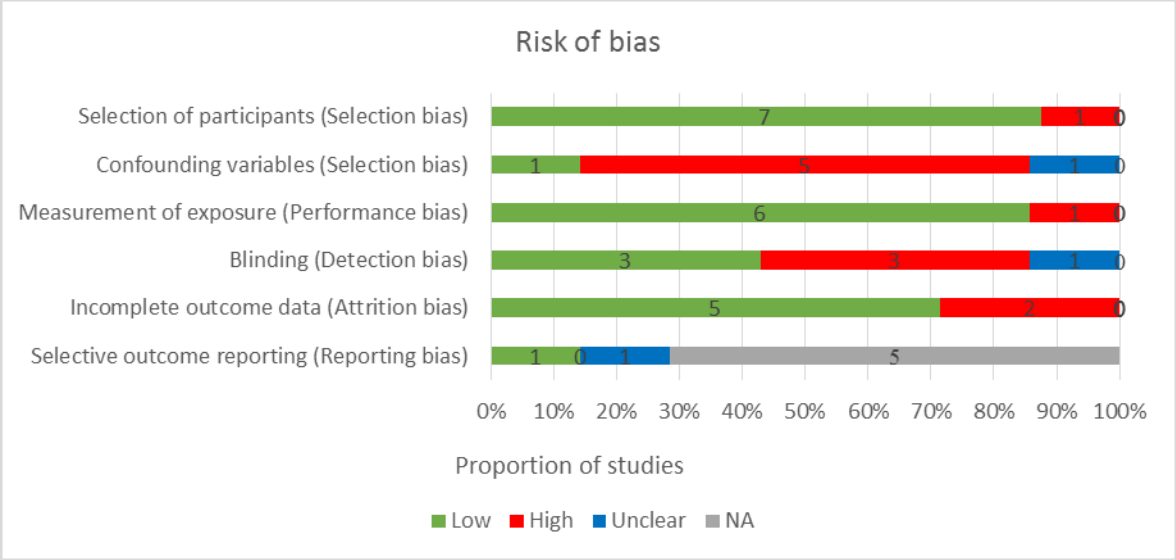
labour to assess whether IAP can prevent them. However, IAP could also cause these outcomes, and therefore we have reported on these outcomes in this review (see **Appendix 27**).[95,101-107,109,110]

Question 18 and 19: Methodological quality

The methodological quality of the seven included observational studies, assessed by RoBANS tool[28] is summarised in **Risk of** bias judgements: Low= The study methods for the respective domain are unlikely to alter the results; High= The study methods for the respective domain are likely to alter results; Unclear= It is uncertain whether study methods in the respective domain were likely or unlikely to alter results.

Figure 6 and **Appendix 29**. Risk of bias was considered high in two or more domains in four of seven studies[40,77,80,81] (57%) and in one domain in the remaining three studies[82-84] (43%). No study was judged as low or unclear risk of bias in all six domains. **Risk of** bias judgements: Low= The study methods for the respective domain are unlikely to alter the results; High= The study methods for the respective domain are likely to alter results; Unclear= It is uncertain whether study methods in the respective domain were likely or unlikely to alter results.

Figure 6 shows that confounding variables was the area with the greatest risk of bias (5/7, 71% high risk), as confounding factors were not adequately considered during the design and analysis.[40,77,80,81,83] Another issue was that outcome assessments were not blinded in all seven studies; depending on the outcome, the risk of detection bias was judged as high in three studies.[77,81,82] The risk of bias in the included systematic review[85] was assessed by the AMSTAR tool[29] and received an AMSTAR score of 9/11, which indicates a high methodological quality (AMSTAR score 9 – 11) of this paper.



Risk of bias judgements: Low= The study methods for the respective domain are unlikely to alter the results; High= The study methods for the respective domain are likely to alter results; Unclear= It is uncertain whether study methods in the respective domain were likely or unlikely to alter results.

Figure 6. Risk of bias in observational studies addressing question 18 and 19 according to RoBANS[28]

Question 18 and 19: Analysis of the evidence

The previous review[24] concluded, "*No additional RCTs assessing the effects of intrapartum antibiotic prophylaxis (IAP) on EOGBS have been published since the last NSC update report. An updated systematic review confirmed that the existing RCT evidence shows a reduction in the risk of culture confirmed and probable early GBS infection with IAP. However, IAP was not shown by these RCTs to reduce neonatal mortality from GBS or from all causes. In addition, these RCTs were small, with none of the meta-analyses including more than 500 women, and of poor quality. This led the authors to conclude that giving IAP to women colonised by GBS is not supported by conclusive evidence, and that better quality studies are needed. In the context of this uncertainty, and based on the existing evidence and expert consensus, IAP is recommended by US and UK bodies for reducing EOGBS risk in pregnancies identified as being at risk via screening or risk based approaches.*"

The 2016 review did not identify any additional RCTs assessing the effects of IAP on EOGBS since the previous UK NSC report. The included systematic review[85] also did not identify any new RCTs published until March 2014. The systematic review by Ohlsson & Shah (2014)[85] found that the use of IAP did not significantly reduce the incidence of all-cause mortality, mortality from GBS infection or from infections other than GBS (three trials involving 500 women). IAP reduced the incidence of culture-proven EOGBS compared to no treatment (RR 0.17, 95% CI: 0.04-0.74; three trials, 488 infants). There was also a statistically significant reduction in the incidence of probable EOGBS (symptoms and signs of sepsis or pneumonia in a neonate born to a GBS positive mother with negative bacterial cultures from normally sterile body fluids) in neonates whose mothers were treated with IAP compared to no treatment (RR 0.17, 95% CI: 0.03 to 0.91, two trials, 324 infants). Because of the high risk of bias identified in these three small studies conducted more than 20 years ago, Ohlsson & Shah concluded that there is no valid information to inform clinical practice. The authors also state that RCTs in their systematic review may not be reliably used as a basis for generalisable estimates of IAP effectiveness, as some of the populations studied were very specific with exceedingly high rates of EOGBS in the control groups.

The searches identified seven observational studies assessing the effects of IAP on EOGBS. All seven studies reported on the outcome culture-proven EOGBS (question 18, **Appendix 24**). The study by Fairlie et al. (2013) investigated the effectiveness of different antibiotics for IAP as well as different duration and timing of IAP on EOGBS incidence.[84] They found that IAP with penicillin or ampicillin given ≥4 hours prior to delivery is highly effective for prevention of EOGBS in term and preterm (<37 weeks) deliveries (91% and 86% decrease in risk compared to no IAP, respectively). IAP <4 hours or with clindamycin was less effective and not significantly different to no IAP treatment.

The study by Turrentine et al. (2013) investigated the duration of IAP and compared the effectiveness <4 hours of IAP to ≥4 hours of IAP on the diagnosis of clinical neonatal sepsis (defined as early-onset GBS sepsis or clinically suspected GBS infection).[82] When adjusted for maternal age and the duration of rupture of membranes, treatment with ≥4 hours of IAP reduced the risk of infants being diagnosed with clinical sepsis by 65% (adjusted RR 0.35, 95% CI: 0.16–0.79, p=0.01). Infants whose mothers received less than two hours of IAP had the greatest risk of being diagnosed with clinical sepsis (adjusted RR 3.5, 95% CI: 1.3–9.6, p=0.015).

In the remaining five studies,[40,77,80,81,83] statistical analysis of the published data was performed by the reviewers. The number of culture-confirmed EOGBS cases in women with positive antenatal GBS culture receiving adequate (≥4 hours), inadequate (<4 hours) or no IAP prior to delivery was extracted and compared. Due to the low number of EOGBS cases per group no statistical analysis was performed. Taken together, no case of proven EOGBS was observed in women receiving ≥4 hours of IAP in these five studies. One study[80] reported an incidence of proven EOGBS of 1/19 (5.3%) in women with <4 hours of

IAP, while in two other studies[77,81] no case of proven EOGBS occurred in women with IAP <4 hours. In GBS-positive women without IAP, the reported incidence of proven EOGBS was 1/20 (5%)[40] and 3/53 (5.7%),[77] respectively, while the other three studies[80,81,83] did not observe a case of proven EOGBS in 19, 22, and nine women receiving no IAP, respectively.

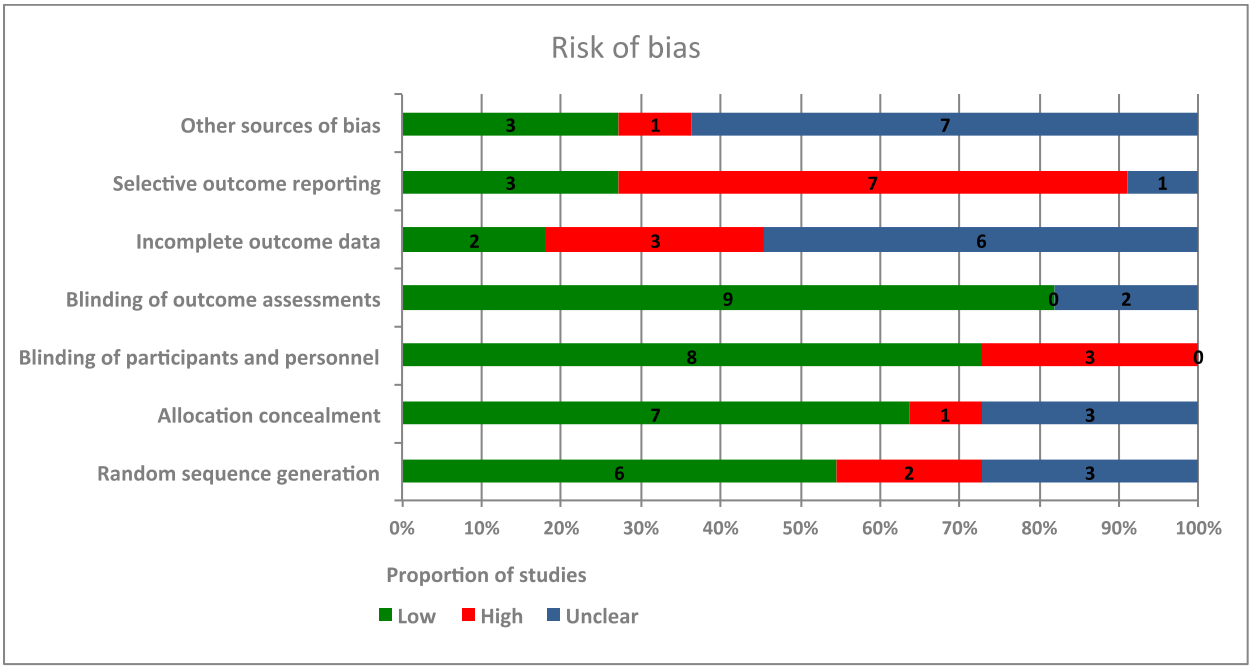
Two observational studies reported on the outcome probable/culture-negative EOGBS (question 19, **Appendix 25**).[81,83] Reviewers conducted statistical analyses on all women who screened positive for GBS. El Helali et al. (2012) reported 5/255 (2.0%) cases of probable EOGBS in women receiving IAP and 1/22 (4.5%) cases in women not receiving IAP corresponding to a RR of 0.43 in IAP-treated women (p=0.39, Fisher's Exact test performed by reviewers).[83] Kojima et al. (2014) reported 0/196 probable EOGBS cases in GBS carrier women receiving greater than or equal to four hours of IAP, 3/69 (4.5%) cases in women receiving less than four hours IAP and no case in nine women receiving no IAP.[81]

No new evidence on the effects of IAP compared to no treatment on all-cause mortality or neonatal mortality from EOGBS was identified.

Question 20: Methodological quality

Risk of bias judgements: Low= Possible bias in the respective domain unlikely to seriously alter the results; High= Possible bias in the respective domain likely to weaken confidence in the results; Unclear= Possible bias in the respective domain raises some doubt about the results.

Figure *7* shows the overall methodological quality of the included RCTs, as assessed by the Cochrane risk of bias tool.[*31*] None of the RCTs were judged as low risk of bias across all domains. Kenyon et al.'s (2008)[96] RCT in the UK specifically investigated the long-term effects of IAP on children. The study had a low risk of bias in all major domains except 'other' biases, as there was a relatively small sample size on which numerous statistical analyses were conducted, a considerable amount of data not being shown, and outcomes were parent reported and children were not individually assessed. The greatest risk of bias amongst these RCTs was in the selective outcome reporting domain, where seven RCTs were at high risk.[95,101-104,107,109] For a number of trials, this was partly or solely because the definition and measurement of side effects were not pre-specified in the methods, but only reported in the results. More than half of the RCTs were rated as unclear risk of bias in the incomplete outcome data domain, as there was substantial missing data, for example, on the adverse effects in the control group. Finally, we found a number of other sources of bias across studies. This included a lack of information on treatment regimens,[102] or details of intention to treat analysis,[105,109] relatively small sample sizes,[96,106] numerous data not being presented,[96,103,104] and inaccuracies in the numbers provided for the participant flow.[107]

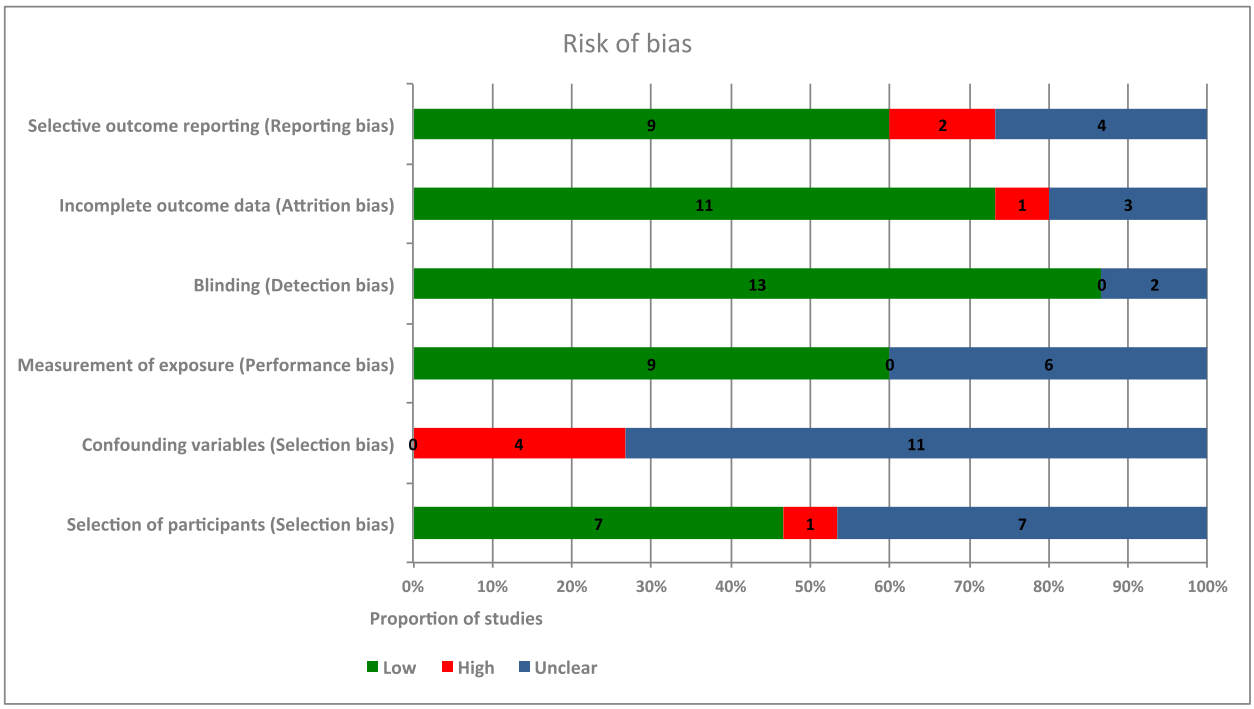


Risk of bias judgements: Low= Possible bias in the respective domain unlikely to seriously alter the results; High= Possible bias in the respective domain likely to weaken confidence in the results; Unclear= Possible bias in the respective domain raises some doubt about the results.

Figure 7. Risk of bias in randomised controlled trials addressing question 20 according to the Cochrane RoB[31]

Similar to the RCTs, there were no observational studies judged as low risk of bias using RoBANS (see **Risk of** bias judgements: Low= The study methods for the respective domain are unlikely to alter the results; High= The study methods for the respective domain are likely to alter results; Unclear= It is uncertain whether study methods in the respective domain were likely or unlikely to alter results.

Figure 8).[28] Confounding variables was the domain with the highest concern, as four studies were rated as high risk,[86,92,98,100] none were low risk, and 11 were unclear risk of bias.[63,87-91,93,94,97,99,108] Likewise, the selection of participants was also unclear across seven studies,[63,87,88,94,98,99,108] as there was no mention of important baseline characteristics or how participants were selected. Some baseline and/or confounding variables were accounted for in the study design or at least reported, while others, such as maternal risk factors, prenatal antibiotics, and caesarean sections, were not.



Risk of bias judgements: Low= The study methods for the respective domain are unlikely to alter the results; High= The study methods for the respective domain are likely to alter results; Unclear= It is uncertain whether study methods in the respective domain were likely or unlikely to alter results.

Figure 8. Risk of bias in observational studies addressing question 20 according to RoBANS[28]

The 26 studies assessed a range of neonatal and maternal outcomes. A summary on the evidence and methodological quality on each outcome is provided below and in **Appendix 26** and **Appendix 27**.

Question 20: Analysis of the evidence

Gut microbiota

Gut microbiota changes in babies have been associated with long-term health problems, including respiratory and metabolic conditions. Six cohort studies compared the colonisation levels of various microbial groups, at different points in time, in infants whose mothers were treated with IAP to those who were not.[86-88,91,94,97] Some studies also reported the number of colonised infants (see **Appendix 26).** The risk of bias for each study was unclear for at least one domain. None of the studies were at low risk of bias for confounding variables, and one was at high risk of selection bias.[86] The key results are summarised below, however, it should be noted that the evidence on each microbial group was conflicting, and because children were not followed up long enough, it is unclear how these potential differences affect the participants in the short or long term.

Bifidobacterium – Compared to control infants, Aloisio et al. (2014) and Corvaglia et al. (2016) revealed a significantly lower mean colonisation of *Bifidobacterium* in six to seven day old infants whose mothers were treated with IAP for GBS prevention,[86,91] and Arboleya et al. (2015)[87] found a lower percentage of *Bifidobacterium* in 30 day old preterm infants whose mothers were treated with IAP (indication not stated). Conversely, Corvaglia et al. (2016) demonstrated no significant difference in the number of

participants or the amount of colonisation reported for *Bifidobacterium* in 30-day old infants and Jaureguy et al. (2004) in three day olds.[91,94] There was a lower percentage of *Bifidobacterium* colonisation in infants at 90 days whose mothers were treated as identified by quantitative polymerase chain reaction (PCR). However, the statistical results could not be isolated for antibiotics during labour only (some infants were exposed to antibiotics postnatally, and this result was also not identified by cluster analysis).[87]

Lactobacillus – Keski-Nisula et al. (2013)[97] found that there was a lower transmission of *Lactobacillus* in mother-infant pairs treated with IAP for GBS prevention and other indications (1/17, 6%) compared to control mother-infant pairs (13/28, 46%) immediately after birth (OR: 0.08, 95% CI: 0.007-0.80), while Arboleya et al. (2015)[87] showed a significantly lower percentage of *Lactobacillus* colonisation at 30 days. On the other hand, Aloisio et al. (2014) and Corvaglia et al. (2016) did not find significant differences in median *Lactobacillus* colonisation at six to seven days[86,91] or 30 days.[91]

Clostridium – Jaureguy et al. (2004)[94] found a lower median colonisation of *Clostridium* in three day old infants whose mothers were treated with IAP for GBS prevention compared to those who were not, and a lower number of infants in the treated group who were colonised with *Clostridium* compared to the control group (3/25 [12%] versus 7/25 [28%], calculated RR: 0.30, 95% CI: 0.09-0.96). On the other hand, Aloisio et al. (2014)[86] did not find a significant difference in *Clostridium* colonisation levels.

Bacterial phyla – Arboyela et al. (2016)[88] found lower frequency of *Actinobacteria* phylum and *Firmicutes* phylum in preterm infants whose mothers were treated with IAP (indication not stated) compared to those who were not treated.

Neonatal respiratory problems

Four randomised controlled trials investigated respiratory problems in infants whose mothers were and were not treated with IAP for preterm labour.[96,101,105,109] None of the trials found a significant difference between the two groups for wheezing, medication for chest problems, admission for chest problems, ventilation or respiratory distress syndrome. Two trials had a high risk of bias in selective outcome reporting and/or incomplete data.[101,109]

One observational study (Lin et al., 2006)[63] found a significant risk of respiratory distress (44/213 [21%] versus 95/1378 [7%] RR: 2.62, 95% CI: 1.79-3.83) and discharge diagnosis of a respiratory disorder (12/213 [7%] versus 39/1378 [3%] calculated RR: 1.96, 95% CI: 1.04-3.69) in the group treated with IAP for GBS prevention. This study did not have a high risk of bias in any domain and adjusted for a number of confounding variables, including comorbidities during labour. However, it did have an unclear risk of selection and detection bias, and because it was observational there could still be other factors that are related to the higher risk of respiratory distress.

Antibiotic resistance

Five studies reported antibiotic resistance. Four were observational studies and one was a randomised controlled trial. Gordon et al. (1995)[102] reported 0/58 cases of multi-resistant bacterial infections in the group treated with IAP for preterm labour, however, they did not report on number of cases in the control group of their RCT.

Of the four observational studies, two were case control studies,[89,93] one was a prospective cohort study,[94] and one was a retrospective cohort study.[98] There was no detection bias across studies. However, there was a high risk of selective outcome reporting bias in Ashkenazi-Hoffnung et al. (2011),[89]

and a high risk of bias regarding confounding variables in Stoll et al. (2011)[98]. There was also an unclear risk of bias in the remaining studies for confounding variables,[89,93,94] unclear risk of selection bias and bias in the measurement of exposures in Jaureguy et al. (2004)[94] and Stoll et al.,[98] as well as an unclear risk of bias for incomplete data in Stoll et al[98].

Glasgow et al. (2005)[93] found that in 62 infants whose mothers were treated with various IAP drugs (indication not stated), 24 (39%) had ampicillin resistant organisms, compared to 13/120 (11%) infants whose mothers were not treated (OR: 5.7, 95% CI: 2.3-14.3). The authors also reported a significant difference when analysing ampicillin resistant urinary tract infections separately (OR: 4.3, 95% CI: 1.6-11.7). Similarly, Stoll et al. (2002)[98] found that mothers of infants with ampicillin resistant strains of *E. coli* were significantly more likely to have received intrapartum ampicillin than were those with ampicillin-sensitive strains (26 of 28 [93%] versus 1 of 5 [20%], p=0.01).

Ashkenazi-Hoffnung et al. (2011)[89] found a significant difference in the development of first generation cephalosporin resistant UTIs in infants born to mothers treated with IAP for GBS prevention and those who were not (75% versus 23.5%, p=0.04), however, the numbers in this analysis did not add up. The authors also reported non-significant differences in first generation cephalosporin resistant bacteria (75% versus 23.5%, p=0.19) and *E. coli* bacteria separately (60% versus 22.7%, p=0.21), as well as ampicillin resistant bacteria (85% of 17 treated versus 63% of 112 untreated [numbers unclear as they do not add up], p=0.19) and *E. coli* bacteria separately (100% versus 54.5%, p=0.14), however, these numbers also did not add up. The authors found no gentamicin or third generation cephalosporin resistance.

Finally, Jaureguy et al. (2004)[94] investigated colonisation of amoxicillin-resistance *Enterobacteriaceae and aerobic and anaerobic gram-positive bacteria* in the gut of neonates. The authors did not find a significant difference between the number of neonates whose mothers were treated with IAP for GBS prevention compared to neonates whose mothers were not treated being colonised by amoxicillin-resistant *Enterobacteriaceae:* 10/25 (40%) versus 12/25 (48%) (calculated RR: 0.83, 95% CI: 0.44-1.56) and amoxicillin-resistant *E. coli*: 6/25 (24%) versus 11/25 (44%) (calculated RR: 0.55, 95 CI: 0.24-1.25]).

Candidiasis

Two studies reported on the relationship between IAP and candidiasis. Cox et al.'s (1996)[101] RCT showed 27/39 (69%) participants treated for preterm labour with ampicillin and sulbactam followed by ampicillin-clavunate for five days had symptomatic vulvovaginitis caused by *Candida albicans.* There was no report on how many cases were present in the control group, and as such the RCT was at high risk of bias for the selective reporting and incomplete data domains.

Dinsmoor et al. (2005)[92] explicitly studied neonatal and maternal candidiasis in a retrospective cohort study. The authors did not find a significant difference in neonatal thrush between the neonates whose mothers were treated with IAP for GBS prevention and other indications and those who were not (21/173 [12%] versus 18/262 [7%]). They did find a significantly higher risk of maternal thrush in the treated group (22/173 [13%] versus 17/262 [6%], OR: 2.1, 95% CI: 1.08-4.08). However, this study was at high risk of bias for confounding variables, as no consideration was given to confounding variables including administration of antenatal antibiotics. Three domains were also judged to be at unclear risk of bias, including measurement of exposure, blinding, and selective outcome reporting. Furthermore, the diagnosis of thrush was based on participant report and whether treatment was prescribed; the diagnosis was not confirmed by an examination.

Hospitalisation and length of stay

Six studies investigated hospitalisation and length of stay. Four were RCTs that investigated the beneficial impact that IAP could have on reducing the hospitalisation and length of stay from preterm and complicated labour.[101,106,107,109] Three of four of the trials were conducted in the 1980s and 90s, and two or more were at a high risk of bias for incomplete data,[101,106] and/or high risk of bias for selective outcome reporting.[101,107,109]

Three of these RCTs[106,107,109] investigated admission to the neonatal intensive care unit (NICU) or the intermediate and intensive care nursery. Svare et al. (1997) found a significantly lower proportion of admission in the neonates whose mothers were treated compared to neonates whose mothers were not (23/58 [40%] versus 32/51 [63%], calculated RR: 0.63, 95% CI: 0.43-0.93).[109] Rajaei et al. (2006)[107] also found a lower proportion of NICU admission in the treated group compared to the untreated group (14/38 [37%] versus 25/42 [60%], $p<0.05$ reported in the study). This result may have been borderline significant, as the RR calculated by the review authors was 0.62 (95% CI: 0.38-1.01), the risk difference was −22.68% (95% CI: −44.02- −1.34), and p=0.043. On the other hand, McGregor et al. (1986)[106] did not find a significant difference (2/8 [25%] versus 3/9 [33%]) in the number of neonates being admitted to intermediate or intensive care nurseries.

Three trials reported the number of days neonates spent in hospital. Cox et al. (1996)[101] and McGregor et al. (1986)[106] found no significant differences in the mean neonatal ICU days, total days in nursery, or maternal days in hospital between neonates whose mothers were treated with IAP and control groups (see **Appendix 27**). Svare et al. (1997)[109] found that the median number of days in neonatal department were 11.5 days higher in placebo than control (27 days versus 15.5 days), but did not test this difference statistically.

In two retrospective cohort studies,[90,100] this outcome was investigated as a potential harmful impact of IAP for GBS prevention and other indications. Balter et al. (2003)[100] found no difference in the number of infants admitted to NICU (3/81 [4%] versus 7/180 [4%], but of the infants that were hospitalised, infants whose mothers were treated with IAP were hospitalised for longer (56.8 versus 47 hours, p=0.02) than infants whose mothers were not treated. When the length of hospitalisation was categorised as more or less than 48 hours and more or less than 72 hours, only the proportions hospitalised for ≥48 hours was significantly higher in the treated group (14/81 [18%] versus 12/180 [7%] calculated RR: 2.59, 95% CI: 1.26-5.35). However, this study was at a high risk of bias for not adequately accounting for confounding variables. Conversely, Briody et al. (2016)[90] did not find any significant differences in hospitalisation less than two days or less than three days between infants whose mothers were treated with "appropriate IAP" (penicillin or cefazolin) and "inappropriate IAP" (clindamycin, erythromycin, or vancomycin) for GBS prevention.

Neonatal bacterial infections

There were four randomised controlled trials,[102,105,109,110] three case-control studies,[89,93,108] and one cohort study[98] that reported on neonatal bacterial infections. The four randomised controlled trials investigated neonatal infections as an outcome when assessing the benefit of IAP in preventing preterm labour. Nadisauskiene et al. (1996)[110] found a significantly lower proportion of neonatal infections in the group of infants whose mothers who were treated with IAP compared to those who were not (4/44 [9%] versus 38/58 [21%] calculated RR: 0.14, 95% CI: 0.05-0.36). None of the other studies found a significant difference in neonatal pneumonia, sepsis, meningitis, all infections or positive cultures. Two of the

trials[102,109] had a high risk of bias in one or more domain and three[105,109,110] had an unclear risk of bias in one or more domain.

Of the four observational studies investigating neonatal infections in infants whose mothers were treated compared to infants whose mothers were not treated, one had a high risk of bias in confounding variables,[98] and two had a high risk of bias in selective outcome reporting.[89,108] Glasgow et al. (2005)[93] found a significantly higher proportion of late-onset bacterial infections in infants whose mothers were treated with all IAP (indication not stated), although both groups had high rates of infection (37/62 [60%] versus 53/120 [44%] OR: 1.96, 95% CI: 1.05-3.66). This association was attributed to broad spectrum IAP as opposed to penicillin IAP, as when the drug treatments were compared separately, only those treated with broad spectrum IAP compared to no broad spectrum IAP had significantly higher infections (OR: 4.95, 95% CI: 2.04-11.98). The authors also found a significantly higher number of late-onset meningitis, omphalitis, and bacteraemia without UTI in the treated group (OR: 25, 95% CI: 1.8-346).

On the other hand, Stoll et al. (2002)[98] found no significant difference in all cause sepsis (63/3,554 [2%] versus 21/1,893 [1%], OR: 1.1, 95% CI: 0.6-1.8]) or *E. coli* early-onset sepsis (58/3,554 [2%] versus 26/1,893 [1%], OR: 1.0, 95% CI: 0.6-1.6) between neonates whose mothers were treated with IAP (indication not stated) and those that were not. When comparing IAP given within 72 hours of delivery compared to no IAP within 72 hours, the authors did find a significant difference in early-onset *E. coli* sepsis with ampicillin (but this became non-significant when controlling for gestational age and the interval between membrane rupture and delivery). Total early onset sepsis was not significantly associated with IAP use. Ashkenazi-Hoffnung et al. (2011)[89] found no significant difference in late-onset serious bacterial infections (8/17 [47%] versus 17/178 [10%], OR per dose of IAP: 5.1, 95% CI: 0.01-93.11) and neither did Sinha et al. (2003)[108] in the proportion of bloodstream infection (RR: 0.20, 95% CI: 0.011-3.6), pneumonia (RR: 2.5, 95% CI: 0.43-14.0), or any infection syndrome (RR: 1.0, 95% CI: 0.38-2.9). The treated group was given IAP in these studies for GBS prevention.

Anaphylaxis and other side effects

Seven RCTs reported on anaphylaxis and other side effects to antibiotics.[95,103-107,109] The RCTs investigated the effectiveness of IAP to prevent preterm labour or post-partum infection. Five RCTs[95,103,104,107,109] were at high risk of bias and one was at unclear risk of bias for selective reporting,[106] while six were at unclear risk of bias for incomplete outcome data,[95,103-105,107,109] and other sources.[103-107,109]

Three RCTs reported no differences in the side effects between treated and control groups. McGregor et al. (1986)[106] did not find any differences in the number of women who suffered from nausea or vomiting (1/29 in each group), while Rajaei et al. (2006)[107] stated that they found no significant differences in nausea, vomiting, hot flushes, decreased deep tendon reflexes, emotional disturbances, or drug intolerance between groups. Keuchkerian et al. (2005)[105] and Svare et al. (1997)[109] did find more side effects (palpitations, flushes, nausea and vomiting[105] and undefined[109]) in treated compared to control groups, but these did not reach statistical significance (2/47 [4%] versus 0/49 [0%][105] and 4/59 [7%] versus 1/51 [2%][109]).

Keettel et al. (1949, 1950)[103,104] and Kampikaho et al. (1993)[95] only reported side effects in the treatment group. Kampikaho et al. (1993)[95] reported no undefined side effects from streptomycin or penicillin (0/330 women). Keettel et al. (1949)[104] found seven mild urticaria (2%), two general urticaria (0.4%), five local allergic manifestations (1%), and no abscess formations (0%) in 465 treated participants, as well as

relatively uncommon discomfort at the site of injections which was never severe or persistent. In 1950, Keettell et al.[103] found one general urticaria (0.3%), one local allergic manifestation (0.3%), and no abscess formations in 382 treated participants.

Bowel problems

Three RCTs reported bowel problems. Kenyon et al. (2008)[96] compared all bowel disorders in children aged seven years old whose mothers received any erythromycin (erythromycin alone or combined with amoxicillin-clavulanate) to no erythromycin, and also compared any amoxicillin-clavulanate (alone or with erythromycin) to no amoxicillin-clavulanate (co-amoxiclav) for preterm labour. The authors found that any erythromycin significantly increased the risk of all bowel problems compared to no erythromycin (64/1,611 [4%] versus 38/1,562 [2%], OR: 1.66, 95% CI: 1.10-2.49), even when adjusting for maternal, social class, and other factors. On the other hand, bowel problems did not significantly differ in the any co-amoxiclav group from the no co-amoxiclav group (54/1,587 [3%] and 48/1,586 [3%] respectively). This trial was rated low risk of bias on all domains, except an unclear risk of other sources of bias, as some data were not shown, an extensive number of analyses were conducted on relatively small number of cases, and parents reported on whether their children had bowel problems in a questionnaire and this was not confirmed through individual assessment of the children.

Cox et al. (1996)[101] and Gordon et al. (1995)[102] reported *Clostridium difficile* in the women treated with IAP for preterm labour. Cox et al. (1996)[101] reported one case of pseudomembranous enterocolitis caused by *Clostridium difficile* in 39 treated participants (3%), and Gordon et al. (1995)[102] reported no cases of *Clostridium difficile* colitis in 58 treated women. However, these trials did not state whether there were any *Clostridium difficile* cases in the control group and therefore were at high risk of bias for incomplete outcome data. Furthermore these trials were rated as high risk of bias for selective outcome reporting, as the outcome was not specifically defined in the methods, but only reported in the results. The incidence of *Clostridium difficile* has also changed over time that data from the 1990s is not necessarily very relevant to the current situation.

Only Cox et al. (1996)[101] reported on the relationship between IAP and necrotising enterocolitis (NEC) in neonates – it was a randomised controlled trial investigating the effectiveness of IAP for preterm labour and assessed the benefit of IAP on NEC. The authors found 1/42 (2%) of NEC in the control group and 0/40 (0%) cases in the treatment group, which was not significant.

Cerebral palsy

Only Kenyon et al. (2008)[96] investigated the risk of cerebral palsy in their factorial randomised trial comparing children whose mothers received any erythromycin (erythromycin alone or combined with co-amoxiclav) to no erythromycin, and any co-amoxiclav (alone or with erythromycin) to no co-amoxiclav for preterm labour. The risk of cerebral palsy was significantly higher in infants whose mothers who received any erythromycin versus no erythromycin (placebo or co-amoxiclav) (53/1611 [3%] and 27/1562 [2%], OR: 1.93, 95% CI: 1.21-3.09]) or any co-amoxiclav versus no co-amoxiclav (placebo or erythromycin) (50/1587 [3%] and 30/1586 [2%], OR: 1.69, 95% CI: 1.07–2.67). More children who developed cerebral palsy had been born to mothers who had received both antibiotics (35/735 children) than to mothers who received erythromycin only (18/785 children), co-amoxiclav only (15/763 children), or double placebo (12/735 children). Although there is evidence of an excess risk in both antibiotic groups compared with double placebo (OR 2.91, 95% CI: 1·50–5·65), there is insufficient power to exclude an excess risk in those exposed to either drug alone (erythromycin alone: OR 1.42,

95% CI: 0.68–2.98; co-amoxiclav alone: 1.22, 95% CI: 0.57–2.62). Authors found that children with cerebral palsy were born to mothers recruited at earlier gestations and gave birth sooner after enrolment more often than children without cerebral palsy. The duration of time from trial entry to birth was more likely to be less than one day or between one to 10 days for children with cerebral palsy than those without. Children with cerebral palsy were also more likely to have mothers with antibiotic prescription for postnatal infection than those without. They were also more likely to be male, admitted to NICU, and at an increased risk of associated neonatal morbidity. This was a trial rated low on all main domains and adjusted for maternal baseline, social class, and 'other factors' in the analysis, but rated unclear risk of 'other' sources of bias, as some data were not shown, and an extensive number of analyses were conducted on a relatively small number of cases. In addition, parents reported on whether their children had cerebral palsy in a questionnaire and this was not confirmed through individual assessment of the children.

Diabetes

Only Kenyon et al. (2008)[96] investigated the risk of diabetes between any and no erythromycin treatment (0/1611 versus 2/1562), and any and no co-amoxiclav treatment (2/1587 versus 0/1586) for preterm labour. There was no evidence that either of the antibiotics significantly increases the risk of diabetes. However, this was based on only two cases.

Growth and development

Kenyon et al. (2008)[96] investigated functional development in a variety of areas in their RCT. Functional impairment was defined by the mark III Multi-Attribute Health Status classification system, which is derived from the Health Utilities Index and covers the attributes of vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. Compared to no erythromycin, children whose mothers were administered any intrapartum erythromycin for preterm labour had significantly higher 'any' or 'mild' functional impairment (any functional impairment 658/1,554 [42%] versus 574/1,498 [38%] OR: 1.18, 95% CI: 1.02–1.37; mild 372/1,554 [24%] versus 319/1,498 [21%] OR: 1.20, 95% CI: 1.01–1.43) but no significant differences were found for moderate or severe impairment alone. Co-amoxiclav, with or without erythromycin, had no significant effect on functional impairment. When erythromycin alone was compared to placebo, statistical significance was not reached, possibly because of the smaller sample sizes. The authors also investigated behavioural problems, educational attainment, ADHD, and other developmental problems, and did not find any significant differences between any of the treatments and control groups (see **Appendix *26***).

Skin diseases in the children

Wohl et al. (2015)[99] investigated the relationship between IAP (indication not stated) and atopic dermatitis in a retrospective cohort. This study was at unclear risk of selection bias as the response rate was only 43% and not all confounding variables were accounted for. The results showed that compared to no treatment, only participants whose mothers were treated with more than 24 hours of IAP were at a higher risk of atopic dermatitis (6/11 [55%] versus 100/364 [27%] RR: 1.99, 95% CI: 1.13-3.49).

Other outcomes

In addition to the adverse events that were explicitly searched, other potentially harmful outcomes were identified in the included studies. The outcomes investigated in children were low Apgar scores, seizures, hydrocephalus with shunt, mortality, as well as the impact on management and care including blood cultures taken, mechanical ventilation, oxygen, chest radiograph taken, etc., and admission to hospital at the age of approximately six years. Of these outcomes, the only significant differences were a higher proportion of complete blood counts in neonates whose mothers were treated with IAP for GBS prevention and other indications (21/81 [26%] versus 17/180 [9%] calculated RR: 2.75, 95% CI: 1.53-4.92) found in Balter et al. (2003).[100] This study was at a high risk of bias for confounding variables.

Additional maternal outcomes that were investigated were bleeding abnormalities and maternal infection (fever, endometritis, chorioamnionitis, pyelitis, and mastitis). These were investigated in randomised controlled trials to prevent preterm labour and post-partum infection.[95,102-104,110] Some[95,103,104,110] found evidence of a significantly lower rate of maternal infection in women treated with IAP while others did not.[95,102]

Outcomes not found

No evidence was found on the relationship between IAP and the following outcomes: anxiety, asthma, autism, obesity, supra-infections, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, extended spectrum beta-lactamase – producing organisms, and carbapenem-resistant organisms.

Discussion

Study evidence

The searches identified two observational studies with the primary aim of investigating the effectiveness of IAP in preventing EOGBS including 2,606 and 4,782 pregnant women, respectively. In addition, data from five observational studies with another focus were included, but sample sizes from the included subgroups (women with positive GBS culture receiving or not receiving IAP) were small and did not have enough power to detect significant differences in EOGBS incidences. No new RCTs published since 2012 were identified. As mentioned by Ohlsson & Shah (2014), the opportunities to conduct randomised controlled trials have possibly been lost as practice guidelines recommend IAP for pregnant women with positive antenatal GBS screening results or other risk factors.[85] It would be considered unethical to contravene the recommendations and not administer IAP for the purposes of an RCT.

The systematic review resulted in 26 studies that reported the adverse events from IAP. Fifteen observational studies and one RCT explicitly studied the adverse events of IAP. The primary aim in the remaining RCTs was to investigate the effectiveness of IAP. The best quality RCT evidence showed that IAP significantly increased the risk of bowel problems (from erythromycin but not co-amoxiclav), cerebral palsy (for either drug), and mild or any functional impairment (from erythromycin but not co-amoxiclav). However, the applicability of these findings is uncertain, as the drugs investigated were erythromycin or co-amoxiclav given for 10 days or until birth, to a population in preterm labour. The drug recommendation for GBS IAP treatment in the UK is penicillin or clindamycin,[13] given for shorter durations, at or near, term labour. Furthermore, the plausible biological mechanisms through which IAP can cause the development of cerebral palsy are unknown. There was also evidence from one study that IAP could increase childhood atopic dermatitis (when IAP was > 24 hours). Although 84% of the treated

group received penicillin, applicability is somewhat unclear, as the indication for IAP in this study was unknown, and only a duration of IAP >24 hours increased atopic dermatitis, which is above the average length of labour. Furthermore, this evidence was observational and could be due to confounding factors.

Studies that explicitly included IAP treatment for GBS prevention found that IAP could alter gut microbiota, and increase maternal thrush, neonatal respiratory distress, and length of stay. Regarding the microbiota changes, it is currently unclear what the consequences of the microbiota changes are, as the populations were not followed through to clinical outcomes. Microbiota changes have been associated with respiratory problems such as asthma, metabolic problems such as obesity and diabetes, and autism.[111-113] All of the studies were observational and were at high or unclear risk of bias, and therefore results could be due to confounding factors. Furthermore, it is difficult to separate whether these changes were due to the IAP, GBS, or both.

The evidence in all included populations was inconsistent and unclear for the risk of developing ampicillin resistant colonisation or infections, *Clostridium difficile* bowel problems, NEC, length of stay, microbiota, neonatal infections, and neonatal respiratory problems. Generally the RCTs that investigated the effectiveness of IAP found no increase in the treated group, while the observational studies did find an increase. There was no evidence of significant harm in the immediate side effects of IAP, neonatal thrush, diabetes, ADHD or other developmental problems, behavioural problems, educational attainment, first or third generation cephalosporin, or gentamicin resistance, or maternal infection, in treated compared to untreated groups. No studies were found on anxiety, asthma, obesity, supra-infections, and other antibiotic resistance.

Risk of bias

Risk of bias was considered high in two or more domains in four of seven studies (57%) and in one domain in the remaining three studies (43%) addressing question 18 and 19. No study was judged as low or unclear risk of bias in all six domains. Confounding factors were not adequately considered during the design and analysis in five of the seven observational studies. As outcome assessments were not blinded in all studies, detection bias might have been present in studies where the EOGBS definition included probable or suspected cases with negative culture. Turrentine et al.[82] noted that definition of clinical sepsis was not predefined and as infants born to mothers receiving less than four hours of IAP were considered “at-risk,” the physicians involved in their care may have monitored these infants more closely, performed more tests and ultimately labelled them with the diagnosis of sepsis more frequently. They also mention the possibility of having missed some EOGBS cases who became ill after discharge, but returned to another area hospital for treatment. These studies focussed on culture-proven EOGBS and this can underestimate the actual incidence of infection due to GBS. The presence of antibiotics in neonate’s blood can lead to false negative test results in the presence of infection and overestimate the reduction in EOGBS incidence as a consequence of IAP.

Overall, the observational studies and the RCTs in the systematic review of adverse events from IAP (question 20) were at high or unclear risk of risk bias in more than one domain. Only one RCT[96] did not have a high risk of bias in any domain, and this study had applicability concerns. Seven (64%) of RCTs were at high risk of bias for selective reporting, as many of the outcomes were not pre-specified or only reported in the treated group, while seven studies also had unclear but serious risks of other biases. Furthermore, all but one of the trials aimed to investigate the effectiveness of IAP and might have contained investigator bias. None of the observational studies had a low risk of bias for confounding variables as 11 (73%) studies controlled some, but not all, important confounding variables, while the

remaining four (27%) were at high risk. In these studies, key variables such as the proportion of women with maternal risk factors for infection or who were administered antibiotics during pregnancy were not stated.

Applicability

Generalisability of the results included for question 18 and 19 was limited since all but one study[84] were conducted at a single centre. The two largest trials were conducted in the US; ethnicity was not reported for the secondary analysis performed by Fairlie et al.[84], and was different from the UK in the study by Turrentine et al. (i.e., 50% White, 20% Black, 20% Hispanic).[82] The study by Fairlie et al. (2013) performed a secondary analysis of data collected in 10 USA states 13-18 years ago (1998/1999 and 2003/2004). During 1998/1999, a risk-based approach was in place and indications for IAP may have been different, reducing the generalisability of results to screen-detected populations. Similarly, in the review on adverse events, all studies except one RCT[96] was conducted outside the UK. All but three of the RCTs were conducted more than 19 years ago. Due to the changing susceptibility profile of GBS over time and between hospitals and countries the estimates for IAP effectiveness might be not applicable to a current UK setting.

With respect to the drug treatments in the review on adverse events, the most relevant results for GBS screening are studies where IAP was given for GBS prevention, using penicillin, ampicillin, or clindamycin, given the UK recommendations.[13] As stated above, Kenyon et al., which was the best quality evidence, was conducted in the UK in 2008, and investigated erythromycin or co-amoxiclav, administered for preterm labour, and the treatment was given for 10 days or until birth. IAP for GBS would be penicillin or clindamycin given for shorter durations, at or near term, and therefore the findings may not be applicable to current practice.

Consistency

With respect to the effectiveness of IAP, the two included observational studies with adequate sample size and designed to estimate the effectiveness of IAP[82,84] consistently reported that IAP (penicillin or ampicillin in 100% and 89% of women, respectively) for at least four hours prior to birth was effective (89% risk reduction versus no treatment or 65% risk reduction versus IAP less than four hours) in preventing EOGBS. Only one study assessed the effectiveness of intrapartum clindamycin and found no risk reduction for EOGBS compared to no IAP treatment.

The evidence on adverse events from IAP lacked consistency in the results of many outcomes across the studies, which may be a result of the moderate or unclear risk of bias in the studies. There was only one RCT that was designed to investigate the harmful effects of IAP, which had the lowest risk of bias across studies, and showed that children of mothers who were treated with erythromycin and/or co-amoxiclav had a higher risk of cerebral palsy compared to those who were not. They also found that children whose mothers were treated with erythromycin were more likely to suffer from bowel problems and functional impairment. However this was compared to mothers who were treated with no antibiotic or co-amoxiclav and lacked the power to compare each antibiotic treatment to no treatment. The only other outcome with no contradictory evidence was atopic dermatitis, which only had evidence from one observational study.

Summary

Criterion 9: Not met

The previous review[24] reported that the criterion on the effectiveness of IAP treatment was partly met as the evidence from an updated systematic review of RCT data was uncertain. Partly met is no longer used as a classification by the UK NSC.

In this review, no new RCTs on the effectiveness of IAP treatment were identified. The included updated systematic review[85] was of high quality and concluded that "*There is lack of evidence from well designed and conducted trials to recommend IAP to reduce neonatal EOGBS.*" Findings from two observational studies suggest that the incidence of proven EOGBS or clinical sepsis is reduced with at least four hours of IAP compared to less than four hours of IAP[82] or no treatment.[84] Patients who receive substandard IAP due to reported penicillin-allergy or IAP less than four hours may not have EOGBS prevented in their neonates. However, these results may well be due to bias in these observational studies, as in one study, the outcome 'clinical sepsis' was not predefined, outcome assessments were not blinded to length of IAP and therefore, detection bias might have been present. Confounding factors were also not adequately considered in study design or analysis. In the other study, the risk of selection bias was high and the applicability of the findings might be reduced, as it was a secondary analysis of data collected in 2003/2004 and for one comparison also including even older data from 1998/1999 before introduction of universal GBS screening in the US. No new evidence on the effects of IAP compared to no treatment on all-cause mortality or neonatal mortality from EOGBS was found. IAP can prevent EOGBS but the effectiveness is uncertain, as is the impact IAP would have on culture negative/probable EOGBS and no new studies help to inform this.

Added to the uncertainty on the effectiveness of IAP, the systematic review found that there is also a high uncertainty on the risk of adverse events as a result of IAP. There is evidence that IAP can cause a variety of harms in mothers and children, however, the majority of the evidence is at risk of bias, unclear, or inconsistent. On the one hand, the best quality RCT evidence with the lowest risk of bias has applicability concerns, as the drug regimen and population may be different to that for GBS, and on the other hand, the most applicable evidence explicitly including GBS prophylaxis, is at high risk of bias. Based on this update review and the systematic review on the harms of IAP, this review concludes that there is a poor evidence base on the benefits and harms of IAP. Therefore, UK NSC criterion 9 was judged as not met as the poor quality evidence precludes an accurate assessment, and the balance of benefits and harms from IAP for the prevention of EOGBS, is uncertain.

4.5 Evidence on the UK NSC criterion addressing the clinical effectiveness of the screening programme (key question 21)

21. What is the clinical effectiveness of GBS screening on EOGBS-related mortality and morbidity, neonatal sepsis and neonatal sepsis-related mortality?

These questions relate to UK NSC criterion 11:

"There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity."

Description of the evidence

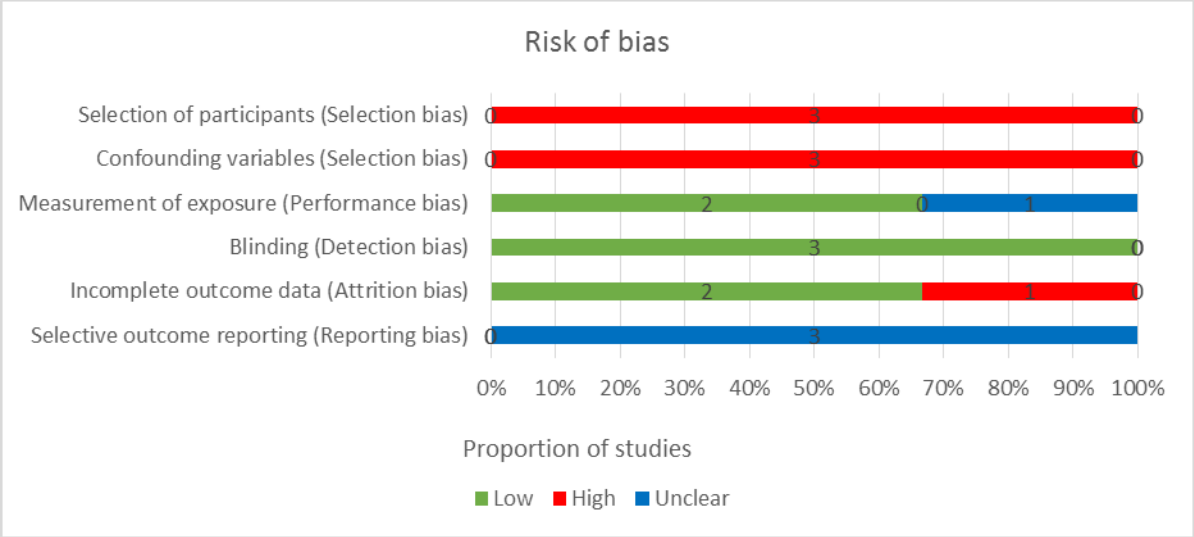
The effectiveness of GBS screening related to criterion 11 was addressed in three studies (**Appendix 12**).[114-116] Study details are summarised in **Appendix 21**. All three studies were observational studies comparing the rates of EOGBS in different periods of time in which different GBS screening strategies were used. The control periods (no screening[115,116] and/or risk-based approach[114,115]) preceded the universal screening periods in all included studies. Two studies were from the US[114,115] and one from Hungary.[116] Universal screening consisted of GBS screening between 30 and 32 weeks of pregnancy with GBS positive women and women with risk factors for the transmission of EOGBS receiving IAP in the Hungarian study;[116] the universal screening strategy was not described in the two American studies.[114,115] IAP consisted of intravenous administration of ampicillin as first choice and erythromycin or clindamycin for penicillin-allergic women in the Hungarian study[116] and was not reported in the two papers from the US[114,115] but one of them mentioned that CDC IAP recommendations were adopted.[115]

Methodological quality of included studies

The methodological quality of the three included observational studies, assessed by RoBANS tool[28] is summarised **Risk of** bias judgements: Low= The study methods for the respective domain are unlikely to alter the results; High= The study methods for the respective domain are likely to alter results; Unclear= It is uncertain whether study methods in the respective domain were likely or unlikely to alter results.

Figure 9 and **Appendix 30**. Risk of bias was considered high in two or more domains in all three studies[114-116] (100%). **Risk of** bias judgements: Low= The study methods for the respective domain are unlikely to alter the results; High= The study methods for the respective domain are likely to alter results; Unclear= It is uncertain whether study methods in the respective domain were likely or unlikely to alter results.

Figure 9 shows that selection of participants and confounding variables were the areas with the greatest risk of bias (3/3, 100% high risk for both areas) as participants of study and control period were not contemporaneous,[114-116] data were collected retrospectively[114,115] and confounding factors were not adequately considered during the design and analysis.[114-116]



Risk of bias judgements: Low= The study methods for the respective domain are unlikely to alter the results; High= The study methods for the respective domain are likely to alter results; Unclear= It is uncertain whether study methods in the respective domain were likely or unlikely to alter results.

Figure 9. Risk of bias in observational studies addressing question 21 according to RoBANS[28]

Analysis of the evidence

The previous review[24] concluded, *"In the absence of RCTs it is difficult to quantify the potential impact of implementing screening for GBS in pregnancy. A systematic review of observational studies found that universal screening reduced the risk of early neonatal sepsis compared with either no screening or a risk-based approach. However, as the groups in these studies are not randomised, or contemporaneous, it is difficult to determine to what extent changes are a direct result of the introduction of screening, as other differences in practice that occurred over the time periods compared may also have had an effect. In addition, there were discrepancies that suggest that the meta-analytical results are not reliable. The US has seen a considerable decrease in the incidence of EOGBS from about 1.7 live births per 1,000 to less than 0.5 per 1,000 live births since guidelines on IAP were introduced in the 1990s. Initially recommendations suggested that IAP could be guided by either universal antenatal bacteriological screening or a risk based strategy. Universal screening was recommended in 2002 in the US, but there was a significant increase in EOGBS between 2003 and 2006 (from 0.34 to 0.40 per 1,000 live births), attributed to increases among black term infants. Additional data collected by the CDC post-2006 suggests that the overall rate of GBS fell after 2006, from 0.39 per 1,000 live births, to 0.26 per 1,000 in 2010 (provisional figures). These more recent figures may not be comparable to the earlier figures, as they differ in the areas included. There is also the suggestion that the changes may reflect a decreased likelihood of cultures being positive due to IAP use, with the culture negative cases of EOGBS sepsis being undetected in these surveillance figures. One study from the US looked at the overall rates of neonatal sepsis based on hospital discharge diagnoses in infants up to the age of three months between 1988 and 2006. It found a steady proportion of culture proven sepsis in this period, which they suggest indicated no appreciable change in false-negative blood cultures after the introduction of IAP. The overall rate of neonatal sepsis did not change significantly over this period, but the proportion of neonatal sepsis cases where Streptococcal bacteria were isolated reduced. It is difficult to identify the specific impact of screening, as the reduction in sepsis in this study seen largely seems to have occurred after the*

introduction of the initial IAP guidance, which suggested that either a risk factor approach or swab results could be used to guide IAP."

The search did not identify any RCTs comparing universal screening for GBS in pregnancy with no screening since 2012. The results of the three included observational studies are summarised in **Table 6** and **Table 7. Table 7**.

The study by Bauserman et al. (2013) reported an incidence of GBS early-onset serious bacterial infections (defined as positive blood, urine [obtained from a catheterization or suprapubic tap], or CSF culture within the first 3 postnatal days) of 3.5 per 1,000 admissions to 322 neonatal intensive care units (NICUs) in the USA over a five year period using a risk-based approach.[114] After the introduction of universal GBS screening, the incidence of GBS early-onset serious bacterial infections decreased to 2.6 per 1,000 admissions to the same 322 NICUs over a nine-year period. On multivariate regression (predictors: gestational age, sex, race, inborn status, five minute Apgar, ventilator support on the first postnatal day, prenatal steroid exposure, prenatal antibiotic exposure, and mode of delivery), the odds of developing EOGBS were lower (OR: 0.69; 95%CI: 0.59-0.80; p<0.001) in the time period with universal screening. EOGBS mortality was 4% in both time periods.

The study by Ecker et al. (2013) compared early-onset neonatal GBS infections in a large, regional tertiary care centre in the USA during three time periods: 1990-1995 (six years) when no formal IAP guideline was followed, 1996-2002 (seven years) when IAP was primarily risk-factor based, and 2003-2007 (five years) when IAP was based on universal screening.[115] The incidence of EOGBS (including blood, urine and CSF infections within the first seven days) decreased from 2.06 per 1,000 live births with no formal IAP guideline to 0.96 per 1,000 live births with risk-based approach and 1.11 per 1,000 live births with universal GBS screening (p=0.02). The mortality from all early-onset infections was 11.4% (12/105), 15.5% (11/71) and 13.6% (6/44) and did not differ between the three periods. Seventy-eight percent of babies with EOGBS over the whole study period (1990-2007) were African-American, whereas they accounted for about 64% of the NICU population during this time.

The study by Horvath et al. (2013) compared EOGBS infections and EOGBS mortality in a teaching hospital in Hungary between a decade (1984-1994) when no screening and no IAP were performed and a 17-year period with universal GBS screening performed between 30 and 32 weeks of pregnancy.[116] Definite EOGBS disease was diagnosed when blood, CSF, urine, tracheal aspirate, or lung tissue were found positive for GBS. Significant decreases in the incidence of all EOGBS infections, GBS sepsis and GBS pneumonia (p=0.001 for all three comparisons) but no change in other GBS infections were observed in the later time period with universal screening. The mortality of EOGBS decreased from 19.5% (29/149) to 1.6% (1/63); mortality from GBS sepsis alone decreased from 93.5% (29/31) to 12.5% (1/8).

Discussion

Study evidence

Overall, three studies evaluated the effectiveness of universal GBS screening versus a risk-based approach (two studies) and/or no screening (two studies). A key weakness across all included studies was the study design. In all three studies, groups being screened or not screened were not randomly allocated and were not from the same time period; the control group (risk-based approach and/or no screening) preceded the period with universal GBS screening (uncontrolled before-after study or historical control study).

Risk of bias

Risk of bias was high in two or more domains in all three studies. There was high risk of selection bias and confounding factors were not adequately controlled for in any study. Therefore, the reported benefits of universal GBS screening might be due to differences in the proportion of women with risk factors for GBS infection, proportion of black women, or adherence to screening guidelines. As there was no contemporaneous control group, it is unknown how the EOGBS rates would have fluctuated over time without introduction of universal screening.

Applicability

Population generalisability may be a limiting factor as the epidemiology of GBS and other population characteristics may be different in the UK compared to the USA and Hungary. Two of the three studies report experiences from a single centre only.[115,116] Universal screening strategy, risk-based strategy, and IAP treatment regime in the two studies from the US[114,115] were not described; therefore the applicability to our review question or to the UK risk-based prevention strategy is unclear. The study by Horvath et al. (2013) performed antenatal GBS screening earlier than 35-37 weeks (at 30-32 weeks of gestation) to meet the needs of the estimated 10% of women who go into premature labour in Hungary. The applicability of the results for a GBS screening programme in the UK performed at 35-37 weeks of gestation is consequently reduced. The reported outcome in the study by Bauserman et al. (2013) was the number of EOGBS cases per 1,000 admissions to 322 NICUs in the US; the impact of universal GBS screening and IAP for the whole population of live born babies is therefore unclear. Furthermore, in all three included studies, the EOGBS definition was broad and included positive urine culture; in two of the studies the method of obtainment for urine was unclear (collection by catheter reduces risk of contamination).

Consistency

All three observational studies reported consistently a decreased incidence of EOGBS with universal GBS screening compared to an era before introduction of universal GBS screening, but benefits compared to a risk-based approach are less consistent. While Bauserman et al. (2013) reported lower odds of developing EOGBS using multivariate regression (OR 0.69,; $p<0.001$) in the period with universal GBS screening compared to the period with a risk-based approach, findings from Ecker et al.[115] suggest that the incidence of culture-positive EOGBS decreased after introduction of a risk-based approach but was not further reduced when universal GBS screening was introduced. Results on the impact of universal GBS screening on EOGBS mortality are inconsistent. The two studies conducted in the USA did not find a change in the EOGBS mortality rate or mortality rate from all early-onset infections between periods with and without universal GBS screening while the Hungarian study reported decreased EOGBS mortality rates after introduction of universal GBS screening compared to no screening. Other changes (i.e. improved clinical practice) and natural fluctuations may have occurred over the study periods that differed between the US and Hungary and may have affected EOGBS mortality.

Summary

Criterion 11: Not met

The previous review[24] reported that the criterion on the effectiveness of universal antenatal culture screening for maternal GBS carriage is not met as there is only observational evidence (no RCTs) assessing the impact of screening on mortality and long term morbidity caused by GBS is uncertain. This update review did not identify any RCTs published since 2012. Risk of bias was high in the three included observational studies as study and control groups were not contemporaneous and confounding factors like proportion of women with risk factors, differences in ethnicity, changes in clinical practice, adherence to screening policy were not adjusted for in the study design or analysis. It is therefore difficult to assess the impact of implementing universal screening for GBS in pregnancy, as other changes may have occurred over the study periods that affected the incidence and mortality of EOGBS. Other changes might also explain the inconsistent results on the impact of universal GBS screening on EOGBS mortality between the two US studies and the Hungarian study. The evidence analysed in this updated review supports the previous judgement.

Table 6. Clinical effectiveness of GBS screening, Outcome EOGBS incidence (review question 21).

Study	EOGBS incidence	Effectiveness	Notes / comments
Bauserman 2013, USA[114] Before (1997-2001): Risk-based screening for GBS & IAP. After (2002-2010): Universal screening & IAP. Total population (1997-2010): 716,407 admissions to 322 NICUs.	**Culture-positive EOGBS** 3.5 per 1,000 admissions 2.6 per 1,000 admissions	**OR (95% CI)** 0.69 (0.59-0.80) p<0.001 (multivariate regression*).	*Predictors: gestational age, sex, race, inborn status, 5-minute Apgar, ventilator support on first postnatal day, prenatal steroid exposure, prenatal antibiotic exposure, mode of delivery. IAP: NR EOGBS: GBS positive blood, urine (obtained from catheterization or suprapubic tap), or CSF culture within the first 3 postnatal days. Cultures positive for same organism within 21-day period considered as single episode of infection.
Ecker 2013, USA[115] Before (1990-1995): No formal IAP guideline, n=18,962 live births. 1996-2002: IAP primarily risk-factor based, n=13,557 live births. After (2003-2007): IAP based on universal screening, n=9,919 live births.	**Culture-positive EOGBS** 2.06 per 1,000 live births 0.96 per 1,000 live births 1.11 per 1,000 live births	OR NR p=0.02 (ANOVA)	IAP: NR EOGBS: Positive blood, urine, or CSF cultures from infants ≤7 days. For infants with more than one early-onset infection episode, only the first episode was considered for analysis.
Horvath 2013, Hungary[116] Before (1984-1994): No GBS screening, no IAP, n=19,722 newborns. After (1995-2011): GBS screening at 30-32 weeks; GBS positive women and women with risk factors received IAP, n=25,857 neonates.	**Definite EOGBS** *7.55* per 1,000 live births GBS sepsis 31 (0.16%) GBS pneumonia 88 (0.45%) Other GBS infection 30 (0.15%) *2.44* per 1,000 live births GBS sepsis 8 (0.03%) GBS pneumonia 19 (0.07%) Other GBS infection 35 (0.14%)	**OR (95% CI)** 0.36 (0.26-0.49); p=0.001 0.27 (0.12-0.58); p=0.001 0.19 (0.11-0.32); p=0.001 0.97 (0.58-1.62); p=0.90	IAP: Ampicillin. Erythromycin or clindamycin intravenously in patients allergic to penicillin. Definite EOGBS: Clinical signs of GBS disease and/or if blood, CSF, urine, tracheal aspirate, or lung tissue positive for GBS.

ANOVA, analysis of variance; CI, confidence interval; CSF, cerebrospinal fluid; EOGBS, early-onset Group B Streptococcus disease; GBS, Group B Streptococcus; IAP, intrapartum antibiotic prophylaxis; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio. *Numbers in italics were calculated by reviewers.*

Table 7. Clinical effectiveness of GBS screening, Outcome EOGBS mortality and total mortality (review question 21).

Study	EOGBS mortality	Mortality	Notes / comments
Bauserman 2013, USA[114] Before (1997-2001): Risk-based screening for GBS & IAP. After (2002-2010): Universal screening & IAP. Total population (1997-2010): 716,407 admissions to 322 NICUs.	17/381 (4%) 55/1370 (4%)	NR NR	*Predictors: gestational age, sex, race, inborn status, 5-minute Apgar, ventilator support on the first postnatal day, prenatal steroid exposure, prenatal antibiotic exposure, mode of delivery. EOGBS: GBS positive blood, urine (obtained from catheterization or suprapubic tap), or CSF culture within the first 3 postnatal days. Cultures positive for same organism within 21-day period considered as single episode of infection.
Ecker 2013, USA[115] Before (1990-1995): No formal IAP guideline, n=18,962 live births. 1996-2002: IAP primarily risk-factor based, n=13,557 live births. After (2003-2007): IAP based on universal screening, n=9,919 live births.	**All early-onset infections** 12/105 (11.4%) 11/71 (15.5%) 6/44 (13.6%) (not significant)	NR NR NR	EOGBS: Positive blood, urine, or CSF cultures from infants ≤7 days. For infants with more than one early-onset infection episode, only the first episode was considered for analysis.
Horvath 2013, Hungary[116] Before (1984-1994): No GBS screening, no IAP, n=19,722 newborns. After (1995-2011): GBS screening at 30-32 weeks; GBS positive women and women with risk factors received IAP, n=25,857 newborns.	29/149 (19.5%) GBS sepsis 29/31 *(93.5%)* 1/63 (1.6%) GBS sepsis 1/8 *(12.5%)*	NR NR	IAP: Ampicillin. Erythromycin or clindamycin intravenously in patients allergic to penicillin. Definite EOGBS: Clinical signs of GBS disease and/or if blood, CSF, urine, tracheal aspirate, or lung tissue were found positive for GBS. Probable EOGBS: Clinical signs of GBS disease and at least 1 of the following: increased or decreased blood neutrophil count; high count of immature neutrophils; high immature-to-total neutrophil ratio; and abnormal CSF findings (i.e., increased protein, decreased glucose levels, pleocytosis).

CI, confidence interval; CSF, cerebrospinal fluid; EOGBS, early-onset Group B Streptococcus disease; GBS, Group B Streptococcus; IAP, intrapartum antibiotic prophylaxis; NR, not reported; OR, odds ratio. *Numbers in italics were calculated by reviewers.*

4.6 Evidence on the UK NSC criterion addressing the cost effectiveness of the screening programme (key question 22)

22. What is the cost effectiveness of GBS screening in the UK?

These questions relate to UK NSC criterion 14:

"The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource."

Description of the evidence

Our electronic searches did not identify any new studies on the cost-effectiveness of GBS screening in the UK related to criterion 14 since 2012.

Analysis of the evidence

The previous review[24] concluded, "*The update search identified no new cost-effectiveness estimates relevant to a UK setting published since the previous update report. One cost study has estimated that EOGBS is associated with an additional health and social care cost of about £3,000 in the first two years of an infant's life in England. These costs have not yet been incorporated into a cost-effectiveness model. A major cost driver identified in this study was prematurity, and the authors suggested that the needs of premature infants with GBS should be specifically addressed*."

The update search identified no new cost-effectiveness estimates of universal GBS screening relevant to a UK setting published since 2012.

Summary

Criterion 14: Not met

The previous review[24] reported that the criterion on the effectiveness of GBS screening was not met as there were no new cost-effectiveness estimates relevant to the UK since the prior review which concluded that there are aspects to screening for GBS which are not easy to incorporate in a cost-effectiveness model, such as *"the effect of widespread use of antibiotics on the development of antibiotic resistance and the impact this will have; the impact of increased medicalisation of birth on maternal and neonatal outcomes; and the effect of very rare but potentially catastrophic anaphylaxis in labour."*

As the 2016 update review did identify no new cost-effectiveness estimates of universal GBS screening relevant to a UK setting published since the previous UK NSC update report, we conclude that the criterion on the cost-effectiveness of GBS screening remains not met.

5. Overall discussion

This report examined 22 key questions relating to the effectiveness and appropriateness of antenatal screening for maternal GBS carriage. These 22 questions correlated to the following five UK NSC criteria:

1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

4. There should be a simple, safe, precise and validated screening test.

9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care.

11. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity.

14. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

The reviewers used a rapid evidence approach, a literature search on electronic databases, published reports and unpublished data from three surveillance organisations (PHE, BPSU, MBRRACE-UK) in the UK to update the research on majority of the questions. In addition two systematic reviews were conducted to answer two new questions – one investigating the bacterial load and molecular markers predictive of EOGBS (UK NSC criterion 1), and another investigating the adverse events experienced by mother and children after IAP (UK NSC criterion 9).

For UK NSC criterion 1, six new studies including two published reports from PHE and preliminary data from the BPSU found an EOGBS incidence in the UK of 0.41 to 0.57 cases per 1,000 live births, which is similar to the previous review. EOGBS incidence in England and Wales was inversely associated with gestational age at birth. Two studies observed an increase in the overall EOGBS incidence over time, while one of them reported a significant decrease in the EOGBS incidence in babies with a birth weight of less than 2.5 kg, and less than 1.5 kg. While EOGBS incidence has increased, the BPSU data confirmed a significant decrease in the EOGBS case fatality rate from 10.6% in 2000/2001 to 5.2% in 2014/2015. The case fatality rate was inversely associated with gestational age at birth, and prematurity was the only independent risk factor for death and poor outcome at discharge. One study showed that in 55.8% of neonates with EOGBS, at least one maternal risk factor for EOGBS was present. Preliminary BPSU data suggest that national GBS prevention guidelines by RCOG and NICE, which are based on the presence of at least one clinical risk factor, only identify 35-41% of UK and Irish EOGBS cases. Only 44% of those women with RCOG risk factors were then treated with IAP; 50% received IAP for less than two hours and only 25% received IAP for at least four hours. The percentage of EOGBS cases born at term with no RCOG or NICE maternal risk factors ranged from 63% (n=212) to 67% (n=225); this is the cohort that universal screening would try to detect. Similarly, 41.7% (n=10) of EOGBS deaths were in babies born after 35 weeks, and 60-70% (n=6-7) had no RCOG or NICE risk factors. These are the EOGBS deaths that universal screening would try to prevent. Risk factors for a risk-based prevention strategy might have to be refined to identify more mothers at risk of having a baby with EOGBS. The low adherence to the risk-

based prevention policy makes it difficult to identify its impact, particularly as the reasons for the low proportion of women with indication receiving IAP are unknown. The observed lower proportion of EOGBS cases with prematurity or PROM as risk factors as well as the declined EOGBS incidence in premature infants in 2014/2015 compared to 2000/2001 suggests that adherence to the risk-based prevention approach might have varied for the different risk factors, with IAP efforts targeted towards women with particular risk factors.

Five new studies reported that 67-89% of GBS-positive women in the third trimester carry GBS in labour, one new study reported that approximately 58% of colonised mothers at birth without IAP transmit GBS to their neonates, and two studies found that 0.5-6% of colonised neonates will develop EOGBS disease. The conducted systematic review on 19 studies found little evidence on bacterial markers that were significant predictors of EOGBS. Serotype III colonisation in neonates was significantly associated with EOGBS disease compared to serotype Ib and II. Heavy bacterial load was strongly associated with GBS vertical transmission compared to light bacterial load. Heavy bacterial load, compared to light bacterial load, was also more associated with EOGBS than asymptomatic colonisation. Neonatal colonisation was higher in mothers colonised with heavy GBS load compared to light load, while EOGBS was up to 15 times higher in neonates colonised with heavy GBS load compared to light GBS load. However, all of these studies were at a high risk of bias.

Overall, EOGBS is an important health condition, though the natural history and the development from GBS carriage to EOGBS disease remain poorly understood and therefore this criterion is not met. Research is critically required to fill this evidence gap on why mothers transmit GBS and why neonates develop EOGBS disease.

For UK NSC criterion 4, six new studies reported findings consistent with the previous review's conclusion that the criterion for a simple, safe, precise and validated screening test is not met. Results from antenatal culture at 35-37 weeks gestation and intrapartum culture were discordant in up to 28% of initially screen-positive women and up to 9% of initially screen-negative women. It is unclear whether this was due to incorrect test results or represents a real change in GBS colonisation status over time. Furthermore, using a combination of studies that estimate each point in the natural history pathway, this review estimates that approximately only 0.2% of mothers with positive maternal GBS colonisation results at 35-37 weeks and no IAP have a neonate with EOGBS. However, this figure contains larges uncertainties due to the uncertainty present in the estimate for each point in the pathway. Using the number of term EOGBS cases found in BPSU study for one year against population figures, also gives an estimate of 0.2%. The only studies directly measuring this since the last review had large 95% confidence intervals from 0.4-40%, so are not very informative. Although each estimate comes with limitations, the linked evidence estimating around 0.2% is preferred, as it is derived from larger numbers. Therefore, a high proportion of women who remain positive at birth would be overtreated, as they would not transmit GBS to their neonate or have a neonate with EOGBS. Screening at 35-37 weeks would also miss many preterm births, which are at a higher risk of EOGBS.

A more accurate test is required to detect GBS colonisation in labour, GBS transmission from mother to baby, and having a neonate with EOGBS. It may also be worth investigating the predictive value of a test that indicates the degree of GBS colonisation (antenatal and/or in labour) on GBS transmission or EOGBS. Of the currently available tests to detect GBS colonisation in labour at that time, rapid PCR is the most promising, however, PCR comes with substantial drawbacks limiting its usefulness. These include: the test is unable to provide information on antibiotic susceptibility, the technical expertise required for administration, women would be required to come in early enough for test and IAP administration, and that a large proportion of women colonised with GBS even in labour will not transmit GBS to their baby or have a baby with EOGBS.

For criterion 9, an update of a systematic review of RCTs included in the previous review and one new observational study found that IAP reduced the incidence of culture-positive EOGBS by 83% and 89%, respectively, compared to no treatment. Two observational studies also demonstrated that the effectiveness of IAP is reduced in women who receive inappropriate IAP including IAP less than four hours or IAP with clindamycin due to reported penicillin allergy. However, the evidence is from studies that have a high risk of bias. In addition to this uncertainty, the conducted systematic review of 26 studies showed a wide range of harms that could occur in mothers and children as a result of IAP. A large number of pregnant women could be unnecessarily treated and exposed to the potential harms. The best quality evidence from a single RCT found that mothers treated with IAP for preterm labour (erythromycin or co-amoxiclav), were more likely to have children suffering from cerebral palsy compared mothers not treated with erythromycin or co-amoxiclav. Mothers treated with erythromycin only, were more likely to have children who would suffer from mild functional impairment and bowel problems, compared to women not treated with erythromycin.[13] However, this trial has limited applicability as it uses a different drug, a longer drug regimen, and pre-term rather than term labour, so we do not know whether these or similar effects would be found in IAP after screening for GBS. Furthermore, multiple analyses were conducted on a relatively small sample, so this result may simply be due to chance, and the plausible biological mechanisms through which IAP can cause the development of cerebral palsy are unknown. Other potential harms included asthma, colonisation or infection with ampicillin resistant organisms, maternal thrush, atopic dermatitis, microbiota changes, neonatal infections, NEC, respiratory problems, or *Clostridium difficile* bowel problems. However, this evidence was inconsistent and/or at high risk of bias. Of these, microbiota changes, maternal thrush, neonatal respiratory distress, and length of stay were most applicable as there were some studies that explicitly included IAP for GBS prevention. However, these were observational studies at high or unclear risk of bias, and results could be due to confounding variables.

Therefore, the criterion that the intervention is effective and leads to better outcomes is not met due to the uncertainty from the poor evidence base. Better quality evidence is needed to address the effectiveness and adverse events from IAP, although the reviewers recognise the difficulty in conducting an RCT when IAP has become the recommended treatment.

For criterion 11, no RCTs of screening were found in this update review and only three observational studies were included. Results on the effectiveness of universal screening compared to a risk-based approach in reducing EOGBS incidence as well as the impact on EOGBS mortality rates were inconsistent. Risk of bias was high in all three studies as study and control groups were not contemporaneous and confounding factors like proportion of women with risk factors, differences in ethnicity, improvements in clinical practice or adherence to screening policy were not adjusted for in the study design or analysis. Furthermore, in two studies from the USA, details of the screening strategy, risk-based strategy, or IAP treatment regime were not provided, limiting the applicability of results to the UK. Therefore, it remains difficult to assess the impact of implementing a universal screening programme for GBS in pregnancy. Without an RCT on the effectiveness of universal GBS screening in pregnancy, it will remain difficult to answer this question.

For criterion 14, no new evidence on the cost effectiveness of antenatal culture screening for maternal GBS carriage were found. The previous review reported that the criterion was not met, as there were no new cost-effectiveness estimates relevant to the UK since the review before that, which concluded that there are aspects to screening for GBS, which are not easy to incorporate in a cost-effectiveness model. Therefore, criterion 14 on the cost-effectiveness of GBS screening remains not met.

Strengths and limitations

This update review built on a previous UK NSC review of the relevant literature published in 2012 and used a systematic approach to the design of the search strategies and to inclusion and exclusion and quality assessment. Pooling of results was not performed for review questions 1-14, 16-19, and 21-22. A REA was used. The UK NSC requirements for the literature search process of evidence summaries recommend a systematic approach, a minimum of three databases to be searched, and the use of methods to limit the number of references retrieved which are acceptable to the review in question.[117] Because this review adopts the REA approach, searches were limited to three databases, date limits were applied, and only articles in the English language were included. Unpublished literature with the exception of MBRRACE and BPSU, was excluded and no screening of reference lists of eligible articles was performed. Therefore, it is possible that relevant articles might have been missed by this strategy. However, experts in the field checked the list of included studies and suggested 10 further articles. One reviewer performed the sifting and data extraction, with a second reviewer checking a random sample of 20%. Therefore, there is a risk of error occurring in excluding studies and in extracting the data.

Quality appraisal for key question 1-14 (UK NSC criterion 1: Epidemiology and natural history of EOGBS) was not performed and the risk of bias in these studies is therefore unknown. For the other key questions (screening test and treatment/screening programme effectiveness), one reviewer performed quality assessment of all studies and a second reviewer independently assessed a random 20%. Again, this may have resulted in a risk of errors. The use of an untailored QUADAS-2 tool[27] for key questions 16 and 17 might have increased the number of "unclear" ratings.

The systematic reviews did not have any date limit and two reviewers conducted all processes. However, the findings of the review on the adverse events of IAP could not be pooled due to the heterogeneity in the studies. Furthermore, as the reviewers were interested in the results of any adverse events from IAP, they conducted a broad search, which focussed heavily on search terms related to harms or adverse events. Therefore, the reviewers may not have found studies that investigated the outcomes of interest that could be caused by IAP but could also be caused by infection and thus investigated as a benefit of IAP prevention. Nevertheless, the list of included studies was shared with experts and no further studies were found. Studies on the adverse events from caesarean section prophylaxis were excluded due to differences in the regimens for caesarean prophylaxis compared to GBS prophylaxis, and the potential confounding of the surgery itself. Similarly, studies where greater than 10% of women had risk factors for infection, were excluded due to the confounding effect. As a result, harms in such studies that may also be relevant to GBS prophylaxis, might have been excluded.

Finally, in the systematic review on bacterial markers and bacterial load, studies in which more than 10% of participants were given IAP or in which treated participants could not be separated from those who were not, were excluded. This may have resulted in exclusion of more recent studies, as it may be less feasible to conduct studies on untreated women only.

6. Conclusions and implications for policy and practice

This review has found that all five investigated UK NSC criteria are not met. EOGBS is an important health problem. Regarding its natural history, it is still not fully understood why some mothers, but not all, transmit GBS to their neonates. Nor is it known which neonates will develop the disease. A strong relationship was found between increased bacterial load and increased likelihood of GBS transmission from maternal to neonatal GBS colonisation, and from neonatal colonisation to EOGBS disease. Serotype III was also more associated with EOGBS compared to serotype Ia and II. The evidence in this report supports the previous review's conclusion that selective culture at 35-37 weeks gestation is not an accurate predictor of colonisation status in labour, or EOGBS disease in the neonate. Based on these results, a substantial proportion of women would be unnecessarily treated with IAP. The effectiveness and harms of IAP are uncertain due to the high risk of bias in the evidence. Likewise, the clinical effectiveness of a screening programme is also not known, as there is only observational evidence that contains a high risk of bias from confounding variables.

To measure the balance of benefits and harms of introducing universal antenatal culture screening in addition to risk-based prevention, requires RCT evidence, with economic modelling to evaluate the associated costs. However, it is estimated that 0.2% of women who test positive for GBS in the third trimester would go on to have a baby with EOGBS. The positive predictive value of such a screening programme would be very low and overtreatment high.

To improve the balance of benefits and harms for future proposed screening programmes and clinical pathways more research is needed to understand the natural history of GBS, which could help to identify the women who are at most risk of transmitting GBS to their neonates, or the colonised neonates who are at most risk of developing EOGBS. This could help to reduce the number of women treated with antibiotics who are at low risk of having neonates with EOGBS. Although this research is required and is worth exploring, it is important to note that it may be unable to identify detectable factors above the current known risk factors that could be operationalised to change practice on who receives prophylaxis. The particular recommendations are:

- Research to reliably predict which mothers with GBS during labour will transmit GBS to the neonate (approximately 58% of GBS positive women in labour will transmit to the neonate) and which mothers will have a neonate that develops EOGBS. The characteristics may include clinical or demographic risk factors in the mother, biochemical or molecular markers, or bacterial load.
- Research to reliably predict which neonates with GBS colonisation will progress to EOGBS disease (even without IAP only 0.5% of newborns with GBS colonisation might progress to EOGBS disease). Similar to above, characteristics may include clinical or demographic risk factors, biochemical or molecular markers, or bacterial load. It may be difficult to identify neonates with GBS colonisation who will progress to EOGBS in a timely and highly accurate manner to rule out the approximately 99% of neonates with colonisation who do not go on to disease. Nevertheless, there may be infant characteristics that give some prediction. However, they would have to offer strong negative predictive value to justify not treating positive infants.
- Test accuracy research to reliably detect GBS colonisation and bacterial load during labour (approximately 27% of GBS positive women at 35-37 weeks were negative during labour, and 5% of GBS negative women at 35-37 weeks were positive during labour). Although the latest in-labour tests may have some practical issues, there may be a feasible option to more accurately measure who is colonised in labour and how heavily.

In addition, future research could also explore the risk factors used in the risk-based prevention strategy with the aim of identifying more EOGBS cases, and treating fewer women whose babies

would not go on to develop EOGBS. The reasons for the low adherence to the risk-based screening policy should also be investigated as only 44% of EOGBS cases with RCOG risk factors are treated with IAP.

Finally, evidence is needed to understand the burden of GBS associated with stillbirth. As this is a burden not amenable to interventions in labour, interventions earlier in pregnancy may be required.

7. Competing interests of authors and advisors

None of the authors have any competing interests.

8. Team members' contributions

The Division of Health Sciences is located within Warwick Medical School. Warwick Medical School brings together experts in clinical and cost effectiveness reviewing, medical statistics, health economics and modelling. All team members checked and agreed to the final version of the report. The team that carried out the work include:

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10. Appendix

Appendix 1. Search strategies for electronic databases

A - Rapid review (question 1-14, 16-19, 21-22)

Search strategies were developed for MEDLINE (Ovid) and were adapted appropriately for other databases: MEDLINE In-Process & Other Non-Indexed Citations (Ovid), EMBASE (Ovid), and the Cochrane Library (Wiley).

No.	Searches	Results
1	exp Streptococcus agalactiae/	6938
2	(group b adj streptococc*).ab,ti,tw.	5569
3	"Streptococc* agalactiae".ab,ti,tw.	2354
4	1 or 2 or 3	8857
5	limit 4 to (english language and humans and yr="2012 -Current")	747

B – Question 15, Bacterial load and bacterial molecular markers of GBS transmission and transition

No.	Searches	Results
1	exp Streptococcus agalactiae/	6959
2	(group b adj streptococc*).ab,ti,tw.	5594
3	"streptococc* agalactiae".ab,ti,tw.	2362
4	1 or 2 or 3	8887
5	exp Pregnancy/	789164
6	exp Parturition/	12492
7	exp Labor, Obstetric/	42866
8	exp Delivery, Obstetric/	67635
9	exp Pregnancy Complications, Infectious/	39383
10	exp Infant/	1005015
11	(newborn* or new-born*).ab,ti,tw.	133187
12	"infant*".ab,ti,tw.	313567
13	"neonat*".ab,ti,tw.	200040
14	(babies or baby).ab,ti,tw.	52933
15	(antepartum* or ante-partum*).ab,ti,tw.	4783
16	(intrapartum* or intra-partum*).ab,ti,tw.	6437
17	(prenatal* or pre-natal*).ab,ti,tw.	74296
18	(antenatal* or ante-natal*).ab,ti,tw.	25244
19	"birth*".ab,ti,tw.	245168
20	"pregnan*".ab,ti,tw.	380409
21	"matern*".ab,ti,tw.	193553
22	exp Maternal Health Services/	38614
23	exp Obstetric Labor Complications/	57690
24	(labor or labour).ab,ti,tw.	76068
25	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	1968273
26	exp bacterial load/	3824
27	exp Genetic Markers/	48966
28	"bacteria* load*".ab,ti,tw.	3266
29	"bacteria* count*".ab,ti,tw.	5567
30	Biomarkers/	189109
31	Virulence/	42438
32	Molecular Epidemiology/	9804
33	((heav* or light* or low* or moderat* or intens*) and (colonis* or coloniz* or carriage)).ab,ti,tw.	19278
34	((gene* or molecular* or dna or biological or immunological or chromosome) adj3 (marker* or biomarker*)).ab,ti,tw.	77629
35	pathogenicity.ab,ti,tw.	26353
36	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	390515
37	4 and 25 and 36	598
38	limit 37 to (english language and humans)	483

C – Question 20, Adverse events from IAP

No.	Searches	Results
1	exp Parturition/	12492
2	exp Labor, Obstetric/	42866
3	exp Delivery, Obstetric/	67635
4	exp Obstetric Labor Complications/	57690
5	exp Maternal Health Services/	38614
6	(labour or labor).ab,ti,tw.	76068
7	(intrapartum* or intra-partum*).ab,ti,tw.	6437
8	"birth* ".ab,ti,tw.	245168
9	"matern* ".ab,ti,tw.	193553
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	540367
11	"prophyla*".ab,ti,tw.	123992
12	exp Penicillins/	75560
13	exp Erythromycin/	22499
14	exp Clindamycin/	5127
15	exp Cefazolin/	2479
16	"penicillin*".ab,ti,tw.	47421
17	"erythromycin*".ab,ti,tw.	17627
18	"clindamycin*".ab,ti,tw.	8084
19	"cefazolin*".ab,ti,tw.	3395
20	"ampicillin*".ab,ti,tw.	18556
21	"vancomycin*".ab,ti,tw.	18822
22	exp Vancomycin/	11270
23	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	148841
24	11 and 23	6077
25	exp Antibiotic Prophylaxis/	11228
26	exp Patient Harm/	61
27	exp Product Surveillance, Postmarketing/	12311
28	exp Adverse Drug Reaction Reporting Systems/	6159
29	exp Clinical Trials, Phase IV as Topic/	237
30	exp Poisoning/	142202
31	exp Substance-Related Disorders/	242070
32	exp "Drug-Related Side Effects and Adverse Reactions"/	97426
33	exp abnormalities, drug induced/	14033
34	exp Drug Monitoring/	16238
35	exp Drug Hypersensitivity/	41174
36	exp Postoperative Complications/	452309
37	exp Intraoperative Complications/	43956
38	(toxicity or complication* or noxious or tolerability).ab,ti,tw.	913897
39	(safe or safety).ab,ti,tw.	475595
40	"side effect*".ab,ti,tw.	178719
41	((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ab,ti,tw.	321134
42	(ae or to or po or co).fs.	3375206
43	exp Drug Resistance/	266912
44	exp Microbiota/	7355
45	exp Anxiety/co, de [Complications, Drug Effects]	3689
46	exp Anaphylaxis/ci, co, de [Chemically Induced, Complications, Drug Effects]	4550
47	exp Overweight/ci, co, de [Chemically Induced, Complications, Drug Effects]	40346
48	exp Asthma/ci, co, de [Chemically Induced, Complications, Drug Effects]	13539
49	exp Autistic Disorder/ci, co [Chemically Induced, Complications]	2113
50	"autis*".ab,ti,tw.	25670
51	"diabet*".ab,ti,tw.	429193
52	"obes*".ab,ti,tw.	187476
53	asthma.ab,ti,tw.	111575

54	anxiety.ab,ti,tw.	116916
55	(resistance or resistant).ab,ti,tw.	684815
56	(microbiome or microbiota).ab,ti,tw.	15283
57	"anaphyla*".ab,ti,tw.	21961
58	(overweight or over-weight).ab,ti,tw.	41122
59	exp Clostridium difficile/de [Drug Effects]	1015
60	exp Diarrhea/ci, co, po [Chemically Induced, Complications, Poisoning]	7636
61	("Clostridium difficile" or "c. diff" or "c. difficile").ab,ti,tw.	9329
62	(Antibiotic-associated diarrhoea or Antibiotic-associated diarrhea or Antibiotic associated diarrhoea or Antibiotic associated diarrhea).ab,ti,tw.	856
63	exp Bacterial Infections/ci, co [Chemically Induced, Complications]	107697
64	exp Sepsis/ci, co, to [Chemically Induced, Complications, Toxicity]	14407
65	exp "Length of Stay"/	66548
66	exp Skin Diseases/ci, co, to [Chemically Induced, Complications, Toxicity]	119355
67	exp Respiratory Tract Diseases/ci, co, de [Chemically Induced, Complications, Drug Effects]	175941
68	exp Cerebral Palsy/ci, co [Chemically Induced, Complications]	3976
69	length of stay.ab,ti,tw.	30722
70	(respiratory illness* or respiratory disease*).ab,ti,tw.	24271
71	cerebral palsy.ab,ti,tw.	15298
72	(Neonatal Necrotising Enterocolitis or Neonatal Necrotizing Enterocolitis or nec).ab,ti,tw.	3282
73	exp Candidiasis/ci, co [Chemically Induced, Complications]	4197
74	exp Enterocolitis, Necrotizing/ci, co [Chemically Induced, Complications]	343
75	(yeast infection* or Candidiasis).ab,ti,tw.	12236
76	(suprainfection* or supra-infection*).ab,ti,tw.	42
77	exp Methicillin-Resistant Staphylococcus aureus/de [Drug Effects]	3527
78	exp Vancomycin-Resistant Enterococci/de [Drug Effects]	56
79	exp Inflammatory Bowel Diseases/ci, co [Chemically Induced, Complications]	16058
80	(Inflammatory bowel disease* or Crohn's disease* or Ulcerative colitis).ab,ti,tw.	64765
81	exp "Growth and Development"/de [Drug Effects]	241638
82	(Meticillin-resistant Staphylococcus aureus or Methicillin-resistant Staphylococcus aureus or Meticillin resistant Staphylococcus aureus or Methicillin resistant Staphylococcus aureus or MRSA).ab,ti,tw.	20023
83	(skin disease* or dematologic* disease* or skin condition* or dematologic* condition*).ab,ti,tw.	18665
84	(Vancomycin-resistant Enterococci or Vancomycin resistant Enterococci or VRE).ab,ti,tw.	2945
85	(Extended Spectrum Beta-lactamase or Extended Spectrum Beta lactamase or ESBL).ab,ti,tw.	5417
86	(Carbapenem-resistant Organism or Carbapenem resistant Organism or CRO).ab,ti,tw.	1049
87	"antibiotic*".ab,ti,tw.	235443
88	exp Diabetes Mellitus/ci [Chemically Induced]	6098
89	(growth adj2 develop*).ab,ti,tw.	27853
90	11 and 87	16759
91	24 or 25 or 90	25649
92	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 88 or 89	6107621
93	10 and 91 and 92	1243
94	limit 93 to (english language and humans)	990

Appendix 2. Inclusion criteria by review question

Question	Population	Intervention/ Exposure 1/ Index test	Comparator/ Exposure 2/ Reference standard	Outcome	Study design
Condition and Epidemiology					
1. What is the overall incidence of EOGBS in the UK?	Newborns <7 days in the UK. The population coverage must be regional or national.	No intervention	No comparator	Culture-confirmed EOGBS disease (< 7 days, culture from sterile site)	Systematic review Cross-sectional study Cohort study PHE and BPSU published reports (2012 onwards)
2. What is the distribution of EOGBS by maternal risk factors in the UK?	Newborns <7 days in the UK. The population coverage must be regional or national.	**Exposure 1:** Any maternal factor evaluated for association with risk of EOGBS disease	**Exposure 2:** Any maternal factor evaluated for association with risk of EOGBS disease used as reference categories for exposure 1 group	Culture- confirmed EOGBS disease (< 7 days, culture from sterile site)	Systematic review Cohort study Case-control study PHE and BPSU published reports (2012 onwards)
3. What is the clinical presentation of EOGBS in the UK?	Patients with culture-confirmed EOGBS disease (< 7 days, culture from sterile site) in the UK. The population coverage must be regional or national.	No intervention	No comparator	Clinical presentation	Systematic review Cross-sectional study Cohort study PHE and BPSU published reports (2012 onwards)
4. What is the overall mortality rate attributable to EOGBS in live born babies in the UK?	Newborns <7 days in the UK. The population coverage must be regional or national.	No intervention	No comparator	Death from culture-confirmed EOGBS disease (culture from sterile site < 7 days)	Systematic review Cross-sectional study Cohort study PHE, BPSU, MBRRACE published reports (2012 onwards)
5. How is the mortality attributable to EOGBS distributed by maternal risk factors in the UK?	Patients with culture-confirmed EOGBS disease (< 7 days, culture from sterile site) in the UK. The population coverage must be regional or national.	**Exposure 1:** Any maternal factor evaluated for association with risk of EOGBS death	**Exposure 2:** Any maternal factor evaluated for association with risk of EOGBS death used as reference categories for exposure 1 group	Death	Systematic review Cohort study Case-control study PHE and BPSU published reports (2012 onwards)
6. What short-term morbidities are associated with EOGBS in the UK?	Patients with culture-confirmed EOGBS disease (< 7 days, culture from	No intervention	No comparator	Short-term morbidities	Systematic review Cross-sectional study Cohort study

Question	Population	Intervention/ Exposure 1/ Index test	Comparator/ Exposure 2/ Reference standard	Outcome	Study design
	sterile site) in the UK. The population coverage must be regional or national.				PHE and BPSU published reports (2012 onwards)
7. What proportion of EOGBS cases has long-term mild or severe morbidities?	Patients with culture-confirmed EOGBS disease (< 7 days, culture from sterile site). The population coverage must be regional or national.	No intervention	No comparator	Long term morbidities	Systematic review Cohort study PHE and BPSU published reports (2012 onwards)
8. What is the association between EOGBS clinical presentation and morbidity outcomes?	Patients with culture-confirmed EOGBS disease (< 7 days, culture from sterile site). The population coverage must be regional or national.	Any clinical presentation evaluated for association with EOGBS morbidity outcomes	Any clinical presentation evaluated for association with EOGBS morbidity outcomes used as reference categories for exposure 1 group.	Short and long term morbidities	Systematic review Cross-sectional study Cohort study Case-control study PHE and BPSU published reports (2012 onwards)
9. What proportion of stillbirths is associated with GBS each year in the UK, and does this reliably contribute to estimates of GBS associated mortality?	Stillborn babies at any gestational age in the UK. The population coverage must be regional or national.	No intervention	No comparator	Autopsy or culture-confirmed GBS (culture from a sterile site)	Systematic review Cross-sectional study Cohort study PHE, BPSU, MBRRACE published reports (2012 onwards)
10. What is the relationship between gestational age and GBS-related stillbirths in the UK?	Stillborn babies at any gestational age in the UK. The population coverage must be regional or national.	**Exposure 1:** A gestational age category evaluated for association with GBS stillbirth	**Exposure 2**: A gestational age category evaluated for association with GBS stillbirth used as the reference category for exposure 1 group	Autopsy or culture-confirmed GBS (culture from a sterile site)	Systematic review Cross-sectional study Cohort study Case-control study PHE, BPSU, MBRRACE published reports (2012 onwards)
Natural History					
11. What is the maternal GBS carriage rate in the UK?	Pregnant women in third trimester in the UK	No intervention	No comparator	Selective cultured-confirmed GBS from recto-vaginal swab	Systematic review Cross-sectional study Cohort study (2012 onwards)

Question	Population	Intervention/ Exposure 1/ Index test	Comparator/ Exposure 2/ Reference standard	Outcome	Study design
12. What proportion of antenatal screen positive and screen negative women transition in terms of carriage status at term?	Pregnant women tested for GBS in third trimester using selective culture (on recto-vaginal swabs)	No intervention	No comparator	Full term intrapartum women tested for GBS using selective culture on recto-vaginal swabs	Systematic review Cohort study Nested case-control study (2012 onwards)
13. What proportion of screen positive women at term transmits the bacterium to the baby?	Intrapartum women with selective culture confirmed GBS (from recto-vaginal swabs)	No intervention	No comparator	Culture-confirmed GBS colonised baby (< 7 days, surface culture)	Systematic review Cohort study Nested case-control study (2012 onwards)
14. What proportion of colonised babies is affected by EOGBS?	Culture confirmed colonised neonates (< 7 days, surface culture)	No intervention	No comparator	EOGBS disease (< 7 days, culture from sterile site)	Systematic review Cross-sectional study Cohort study Nested case-control study (2012 onwards)
15. Are there bacterial loads and/or bacterial molecular markers predictive of GBS transmission (from maternal colonisation to neonatal colonisation or EOGBS disease) or GBS transition (from neonatal GBS colonisation to EOGBS disease)?	Culture-confirmed GBS colonised mothers or colonised neonates across any setting. Mothers must be tested for GBS after the onset of the third trimester using vaginal or rectal swabs and selective or standard culture. Neonates must be tested soon after birth using any surface culture.	Any bacterial load or individual bacterial molecular marker evaluated for association with risk of neonatal GBS colonisation or neonatal early-onset GBS disease.	Any bacterial load or individual bacterial molecular marker used as the reference categories for exposures.	Occurrence of GBS colonisation in neonates less than 7 days after birth confirmed by surface culture, or neonates with early-onset GBS disease less than 7 days after birth confirmed by sterile culture.	Prospective or retrospective cohort studies Nested case-control studies Case series if there are insufficient studies.
Test Accuracy					
16. What is the sensitivity and specificity of selective antenatal culture screening tests?	Pregnant women ≥35 weeks	**Index test:** Selective culture from recto-vaginal swabs	**Reference standard:** Selective culture from recto-vaginal swabs in full-term labour	**Target condition:** GBS carriage in full-term labour	Systematic reviews Cross-sectional test accuracy studies Cohort studies (2012 onwards)
17. What is the predictive value of selective antenatal culture screening tests for a) carriage status at term and b) EOGBS disease?	Pregnant women ≥35 weeks	**Index test:** Selective culture from recto-vaginal swabs	**Reference standard:** a) selective culture from recto-vaginal swabs in full-term labour, b) culture confirmed EOGBS	**Target condition:** a) GBS carriage in full-term labour, b) EOGBS disease	Systematic reviews Cohort studies (2012 onwards)

Question	Population	Intervention/ Exposure 1/ Index test	Comparator/ Exposure 2/ Reference standard	Outcome	Study design
			(< 7 days, culture from a sterile site)		
Intrapartum antibiotic prophylaxis (IAP) treatment clinical effectiveness					
18. What is the reported effectiveness of IAP in preventing EOGBS related morbidity and mortality in screen-detected populations?	Intrapartum women with confirmed GBS colonisation at ≥35 weeks (selective culture from recto-vaginal swabs)	IAP	No treatment or placebo	Culture-confirmed EOGBS; Sepsis, pneumonia, meningitis, death from culture-confirmed EOGBS (< 7 days, culture from a sterile site)	Systematic reviews Randomised controlled trials Cohort studies Case-control studies (2012 onwards)
19. What is the reported effectiveness of IAP in preventing culture negative/probable EOGBS in screen-detected populations?	Intrapartum women with confirmed GBS colonisation at ≥35 weeks (selective culture from recto-vaginal swabs)	IAP	No treatment or placebo	Culture negative/probable EOGBS: symptoms or signs of sepsis, pneumonia or meningitis with culture negative GBS (< 7 days, culture from sterile site) but mother is GBS positive	Systematic reviews Randomised controlled trials Cohort studies Case-control studies (2012 onwards)
20. What adverse events do women or children experience after receiving IAP treatment for any prophylactic reason?	Intrapartum women	IAP for a prophylactic purpose only	No treatment or placebo No comparator for case-series.	Any adverse outcomes experienced by the mother or child	Prospective or retrospective cohort studies Case-control studies Randomised controlled trials Case series if there are insufficient studies
Screening clinical- and cost- effectiveness					
21. What is the clinical effectiveness of GBS screening on EOGBS-related mortality and morbidity, neonatal sepsis and neonatal sepsis-related mortality?	Pregnant women in third trimester. The population coverage must be national or regional.	Screening, with antenatal selective culture from recto-vaginal swabs and treating those with positive results with IAP.	No screening	-Culture-confirmed EOGBS; -Sepsis, meningitis, pneumonia, or death from culture-confirmed EOGBS (< 7 days, culture from a sterile site); -Culture negative/probable EOGBS and related	Systematic reviews Randomised controlled trials Cohort studies Case-control studies (2012 onwards)

Question	Population	Intervention/ Exposure 1/ Index test	Comparator/ Exposure 2/ Reference standard	Outcome	Study design
				death: symptoms or signs of sepsis, pneumonia or meningitis with culture negative GBS (< 7 days, culture from sterile site) but mother is GBS positive; -Early-onset sepsis and related death (< 7 days, culture-confirmed from sterile site and/or culture negative with symptoms only).	
22. What is the cost effectiveness of GBS screening in the UK?	Pregnant women in third trimester	Screening, with antenatal selective culture from vaginal or rectal swabs and treating those with positive results with IAP.	No screening	Cost-effectiveness (incremental cost and incremental effectiveness). Effectiveness measured by life years, quality-adjusted life-years (QALYs), deaths avoided, disease avoided.	UK economic evaluations in which the incremental cost-effectiveness ratios (ICERs) were reported. (2012 onwards)

Appendix 3. Data extraction forms for included studies

A – Rapid review (question 1-14, 16-19, 21-22)

STUDY DETAILS	
Study ID	
First author surname year of publication	
Country	
Study design	
Data collection tools	
Study setting	
Number of centres	
Time period / study duration	
Follow-up period	
Funding	
Competing interests / Role of sponsor	
REVIEW QUESTION	
State UK NSC criterion and review question:	
AIM OF THE STUDY	
PATIENT SELECTION	
Inclusion criteria:	
Exclusion criteria:	
Method of patient selection:	
STUDY FLOW	
Screened	
Sample size at baseline (n total)	
Excluded from study (with reason)	
Lost to follow-up/withdrawals (n)	
Included in analysis (n)	
Excluded from analysis (n)	
Included in this review (n) per review question	
Excluded from review (n) with reason	

BASELINE CHARACTERISTICS			
Define groups	**xxx (n=)**	**xxx (n=)**	**Xxx (n=)**
Maternal age Mean ± SD (range), years			
Gestational age Mean ± SD (range), weeks			
Race/ethnicity (n [%])			
At least 1 risk factor for EOGBS (n,[%]) Specify			
Vaginal delivery (n,[%])			
Scheduled C-section (n,[%])			
Other:			

SCREENING	
Define screening test	
Swab site	
Timing of test	
Culture medium (standard or selective)	
Define reference standard for intrapartum GBS carriage status	
Swab site:	
Timing of test:	
Culture medium (standard or selective):	
Define reference standard for EOGBS presence/absence	
EOGBS presence	
EOGBS absence	
IAP TREATMENT & COMPARATOR	
Define IAP treatment (which antibiotic, dose, duration)	
Define appropriate / inappropriate IAP	
Number of women with appropriate / inappropriate / no IAP	

NEONATAL GBS COLONISATION	
Define tests performed in neonates	
Source and type of material / swab site	
Timing of the test	
Culture medium (standard or selective)	
PROPHYLACTIC TREATMENT OF NEWBORNS AT RISK	
Define prophylactic treatment (antibiotic, dose, duration):	
Number of babies treated:	
DEFINITION OF EOGBS / PROBABLE EOGBS / EARLY-ONSET SEPSIS	
EOGBS definition	
Probable EOGBS definition	
Early-onset sepsis definition	
CALCULATION OF EOGBS INCIDENCE	
Nominator	
Denominator	
FACTORS CONTROLLED FOR IN OBSEVRATIONAL STUDIES	
List of factors controlled for	
How controlled	

OUTCOMES	
1) Condition and epidemiology of EOGBS	
1. Incidence UK	
Total number of live births	
Number of identified EOGBS cases	
EOGBS incidence	
Notes / Comments	
1. Serotypes in the UK	
2. Distribution of EOGBS by maternal risk factors	
Low birth weight (definition, n[%])	
Pre-term birth (definition, n[%])	
Intrapartum fever (definition, n[%])	
Prolonged rupture of membranes (definition, n[%])	
Preterm prelabour rupture of membranes (definition, n[%])	
Prelabour rupture of membranes (definition, n[%])	
Previous baby with GBS (n[%])	
GBS carriage in vagina (n[%])	

OUTCOMES	
GBS bacteriuria (n[%])	
Chorioamnionitis (n[%]):	
Other (definition, n[%]):	
Any maternal risk factor (n[%]):	
3. Clinical presentation	
Fever (n[%])	
Difficulty feeding (n[%])	
Difficulty breathing (n[%])	
Irritability (n[%])	
Lethargy (n[%]):	
Other (definition, n[%])	
Age of onset for symptoms	
4. Mortality rate UK	
Direct EOGBS mortality rate	
Overall mortality rate attributable to EOGBS in live born babies in the UK	
5. Distribution of EOGBS mortality by maternal risk factors (state maternal risk factor and n [%] in each)	
Low birth weight (definition, n[%])	
Pre-term birth (definition, n[%])	
Intrapartum fever (definition, n[%])	
Prolonged rupture of membranes (definition, n[%])	
Preterm prelabour rupture of membranes (definition, n[%])	
Prelabour rupture of membranes (definition, n[%])	
Previous baby with GBS (n[%])	
GBS carriage in vagina or urine (n[%])	
Chorioamnionitis (n[%])	
Other (definition, n[%])	
Any maternal risk factor (n[%])	
6. Short term morbidities	
Sepsis (n[%])	
Meningitis (n[%])	
Pneumonia (n[%])	
Other (n[%])	
7. Long-term morbidities	
Mild (n[%])	
Moderate (n[%])	
Severe (n[%])	
Cerebral palsy (n[%])	

OUTCOMES	
Hearing disability (n[%])	
Blindness (n[%])	
Neurological impairment (n[%])	
Functional impairment (n[%])	
Academic underachievement (n[%])	
Delayed development (n[%])	
Other (definition, n[%])	
8. Association between clinical presentation and morbidity outcomes (state clinical presentation and n[%] of each morbidity within)	
9. Stillbirths in the UK	
Number of stillbirths associated with GBS	
Total number of stillbirths per year	
Proportion of stillbirths associated with GBS each year	
Any maternal risk factor (definition, n[%])	
10. Stillbirths by gestational age in the UK	
< 20 weeks (n[%]):	
20-28 weeks (n[%]):	
28-37 weeks (n[%]):	
> 37 weeks (n[%]):	
Other (definition, n[%]):	
1) Natural history	
11. Carriage rate UK	
12. Transition (3rd trimester to intrapartum carriage)	
13. Transmission (Intrapartum carrier to newborn colonisation)	
14. Colonised babies affected by EOGBS	
4) Test accuracy	

2x2 data

	Carriage status at term +	Carriage status at term –
Antenatal culture +		
Antenatal culture -		

	EOGBS +	EOGBS -
Antenatal culture +		
Antenatal Culture -		

15. Reported sensitivity	
15. Reported specificity	

OUTCOMES			
16a. Reported PPV for carriage status at term			
16a. Reported NPV for carriage status at term			
16b. Reported PPV for EOGBS			
16b. Reported NPV for EOGBS			
9) IAP treatment effectiveness			
	(Appropriate) IAP (n=)	**(Inappropriate) IAP (n=)**	**No IAP (n=)**
17. Culture confirmed EOGBS (n[%])			
18. Probable EOGBS (n[%])			
11) Screening effectiveness			
19. Clinical effectiveness			

	Before (xx-xx)	**After (xx-xx)**	**Total (xx-xx)**
EOGBS infections (n[%])			
Total population			
EOGBS incidence			
EOGBS mortality			
Incidence of culture negative/probable EOGBS			
Mortality of culture negative/probable EOGBS			
Early-onset sepsis			
Mortality of early-onset sepsis			
Other reported outcomes			

14) Cost Effectiveness	
20. Cost effectiveness	
Authors' conclusion	
Reviewer's notes	

B - Question 15, bacterial load and bacterial molecular markers of GBS transmission and transition

Review Details	
Reviewer	
Study details	
Study ID Number	
First author surname	
Year of publication	
Country	
Number of centers	
Study design	
Study setting	
Total study duration *(including length of follow up if applicable)*	
Funding *(government/private/manufacturer/other - specify)*	
Aim of the study	
Methods of the study	
Recruitment dates	
Inclusion criteria	
Exclusion criteria	
Participants, Exposures and Outcomes definitions	
General definition of the sample:	
Definition and diagnostic methods for GBS maternal colonisation *(e.g. site of swab, time, culture media)*	
Definition and diagnostic methods for GBS neonatal colonisation *(e.g. site of swab, time, and culture media)*	
Definitions and diagnostic methods for EOGBS neonatal disease *(e.g. site of swab, time, symptoms)*	
Exposure 1	

(Specify general definition of bacterial loads/molecular markers)					
		Exposed group 1	**Exposed group 2**	**Non-exposed group**	**Total**
Definition of each group					
Sample size at baseline (total n)					
Sample size (analysed n)					
Lost to follow-up/withdrawals (n)					
Baseline characteristics	Mean (range or SD) age (years)				
	Mean (range or SD) gestational age (weeks)				
	Female children (n [%])				
	Mean birth weight (range or SD)				
	Race/ethnicity (n [%])				
	Co-morbidity (n [%])				
	Overall (n/N, [% or rate]) maternal OR neonatal GBS colonisation rate (specify)				
	Overall EOGBS rate (n/N, [rate per 1000])				
	Overall (n/N, [% or rate]) transmission or transition (specify mother to neonatal colonisation OR mother to EOGBS disease OR neonatal colonisation to neonatal EOGBS disease)				
	Any treatments received (n [%]) Specify treatment (e.g. IAP)				
	Late onset GBS (n [%])				
	Other				
Exposure 2 *(Specify general definition of bacterial loads/molecular markers)*					
		Exposed group 1	**Exposed group 2**	**Non-exposed group**	**Total**
Definition of each group					

Sample size at baseline (total n)					
Sample size (analysed n)					
Lost to follow-up/withdrawals (n)					
Baseline characteristics	Mean (range or SD) age (years)				
	Mean (range or SD) gestational age (weeks)				
	Female children (n [%])				
	Race/ethnicity (n [%])				
	Co-morbidity (n [%])				
	Maternal GBS colonisation rate (if applicable)				
	Any treatments received (n [%]) Specify treatment (e.g. IAP)				
	Late onset GBS (n [%])				
	Other				
Exposure 3 *(Specify general definition of bacterial loads/molecular markers)*					
		Exposed group 1	**Exposed group 2**	**Non-exposed group**	**Total**
Definitions					
Sample size at baseline (total n)					
Sample size (analysed n)					
Lost to follow-up/withdrawals (n)					
Baseline characteristics	Mean (range or SD) age (years)				
	Mean (range or SD) gestational age (weeks)				
	Female children (n [%])				
	Race/ethnicity (n [%])				
	Co-morbidity (n [%])				
	Maternal GBS colonisation rate (if applicable)				
	Any treatments received (n [%]) Specify treatment (e.g. IAP)				

	Late onset GBS (n [%])				
	Other				
Add information for more exposures as necessary					

Outcomes	
GBS outcomes assessed *(GBS neonatal colonisation, early-onset GBS neonatal disease)*	
Other outcomes *(specify)*	

Results

Outcome *(Specify neonatal colonisation or EOGBS)*	**Exposure 1** *(Specify)*				**Odds ratio, risk ratio, mean difference** *(specify)* **(95% CI)**		**Covariates adjusted for**
	Non-exposed *(Specify)*	**Exposed group 1** *(Specify)*	**Exposed group 2** *(Specify)*	**Total**	**Crude**	**Adjusted**	
Occurred							
Did not occur							
Total							

Outcome *(Specify neonatal colonisation or EOGBS)*	**Exposure 2** *(Specify)*				**Odds ratio, risk ratio, mean difference** *(specify)* **(95% CI)**		**Covariates adjusted for**
	Non-exposed *(Specify)*	**Exposed group 1** *(Specify)*	**Exposed group 2** *(Specify)*	**Total**	**Crude**	**Adjusted**	
Occurred							
Did not occur							
Total							

Outcome *(Specify neonatal colonisation or EOGBS)*	**Exposure 3** *(Specify)*				**Odds ratio, risk ratio, mean difference** *(specify)* **(95% CI)**		**Covariates adjusted for**
	Non-exposed *(Specify)*	**Exposed group 1** *(Specify)*	**Exposed group 2** *(Specify)*	**Total**	**Crude**	**Adjusted**	
Occurred							
Did not occur							
Total							

Add more 2x2 tables for more exposures as necessary						

Authors' conclusion:

Reviewer Notes:

Abbreviations: GBS=group B *Streptococcus*; EOGBS=early-onset GBS; 95% CI=95 percent confidence interval; SD=standard deviation; n=number

C - Question 20, Adverse events from IAP

Review Details	
Reviewer	
Study details	
Study ID Number	
First author surname	
Year of publication	
Country	
Study design	
Study setting	
Number of centers	
Total study duration *(including length of follow up if applicable)*	
Funding *(government/private/manufacturer/other - specify)*	
Aim of the study	
Methods of the study	
Recruitment dates	
Inclusion criteria	
Exclusion criteria	
Recruitment method (e.g. consecutive participants)	
Interventions and participants	
General definition of the sample:	

Intervention arm:	**Antibiotic prophylaxis**	**No treatment**	**Total**
Dose of antibiotic			
Indication for antibiotic			
Antibiotic given			
Duration of antibiotic			

Sample size at baseline				
Sample size analysed				
Lost to follow-up/withdrawals				
Baseline characteristics	Mean (range or SD) age (years)			
	Mean (range or SD) gestational age (weeks)			
	Female children (n [%])			
	Race/ethnicity (n [%])			
	Elective Caesarean section (n [%])			
	Intrapartum fever (n [%])			
	Prolonged rupture of membranes (n [%])			
	Chorioamnionitis (n [%])			
	Co-morbidity (n [%]) specify what this included			
	History of allergy from antibiotic (n[%])			
	Co-intervention (n[%])specify what this included			
	Multiple births (n [%])			
	Mean (rage or SD) birth weight (g)			
	Smoking (n [%])			
	Other (specify)			

Outcomes

Adverse event name	**Definition**	**Time point collected /reported:**	**Measurement**

Results

Adverse event 1 *(specify)*	**Intervention (IAP) [n]**	**Control (Placebo, no treatment) [n]**	**Total**	**Odds ratio, risk ratio, mean difference** *(specify)* **(95% CI)**		**Covariates adjusted for**
				Crude	**Adjusted**	
Adverse event 1 *(specify)* Occurred						

Adverse event 1 *(specify)* Did not occur						
Total						
Adverse event 2 *(specify)*	**Intervention (IAP) [n]**	**Control (Placebo, no treatment) [n]**	**Total [n]**	**Odds ratio, risk ratio, mean difference** *(specify)* **(95% CI)**		**Covariates adjusted for**
				Crude	**Adjusted**	
Adverse event 2 *(specify)* Occurred						
Adverse event 2 *(specify)* Did not occur						
Total						
Add more 2x2 tables and statistical results for more adverse events as necessary						
Authors' conclusion:						
Reviewer Notes:						
Abbreviations: 95% CI=95 percent confidence interval; SD=standard deviation; n=number						

Appendix 4. Quality assessment forms

A – Unadjusted QUADAS-2 tool[27]

QUADAS-2

Phase 1: State the review question:

Patients (setting, intended use of index test, presentation, prior testing):
Index test(s):
Reference standard and target condition:

Phase 2: Draw a flow diagram for the primary study

Phase 3: Risk of bias and applicability judgments

QUADAS-2 is structured so that 4 key domains are each rated in terms of the risk of bias and the concern regarding applicability to the research question (as defined above). Each key domain has a set of signalling questions to help reach the judgments regarding bias and applicability.

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:

- ❖ Was a consecutive or random sample of patients enrolled? Yes/No/Unclear
- ❖ Was a case-control design avoided? Yes/No/Unclear
- ❖ Did the study avoid inappropriate exclusions? Yes/No/Unclear

Could the selection of patients have introduced bias? **RISK: LOW/HIGH/UNCLEAR**

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):

Is there concern that the included patients do not match the review question? **CONCERN: LOW/HIGH/UNCLEAR**

DOMAIN 2: INDEX TEST(S)

If more than one index test was used, please complete for each test.

A. Risk of Bias

Describe the index test and how it was conducted and interpreted:

- ❖ Were the index test results interpreted without knowledge of the results of the reference standard? Yes/No/Unclear
- ❖ If a threshold was used, was it pre-specified? Yes/No/Unclear

Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW /HIGH/UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question? **CONCERN: LOW /HIGH/UNCLEAR**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Describe the reference standard and how it was conducted and interpreted:

- Is the reference standard likely to correctly classify the target condition? Yes/No/Unclear
- Were the reference standard results interpreted without knowledge of the results of the index test? Yes/No/Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW /HIGH/UNCLEAR**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question? **CONCERN: LOW /HIGH/UNCLEAR**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):

Describe the time interval and any interventions between index test(s) and reference standard:

- Was there an appropriate interval between index test(s) and reference standard? Yes/No/Unclear
- Did all patients receive a reference standard? Yes/No/Unclear
- Did patients receive the same reference standard? Yes/No/Unclear
- Were all patients included in the analysis? Yes/No/Unclear

Could the patient flow have introduced bias? **RISK: LOW /HIGH/UNCLEAR**

B - Cochrane Risk of Bias (RoB) tool[31] for randomised studies (question 18-22)

Domain	Risk of bias			Support for judgment
	Low	High	Unclear	*(include direct quotes where available with explanatory comments)*
Random sequence generation	☐	☐	☐	
Allocation concealment	☐	☐	☐	
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	☐	☐	☐	
Blinding of outcome assessments *Assessments should be made for each main outcome (or class of outcomes).*	☐	☐	☐	
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	☐	☐	☐	
Selective outcome reporting	☐	☐	☐	
Other sources of bias	☐	☐	☐	

C - Risk of Bias Assessment Tool for Nonrandomised Studies (RoBANS)[28] for non-randomised studies (question 18-22)

Domain	**Risk of bias** **Low** **High** **Unclear**	**Support for judgment** *(include direct quotes where available with explanatory comments)*
The selection of participants *Selection biases caused by the inadequate selection of participants*	☐ ☐ ☐	
Confounding variables *Selection biases caused by the inadequate confirmation and consideration of confounding variables*	☐ ☐ ☐	
Measurement of exposure *Performance biases caused by inadequate measurements of exposure*	☐ ☐ ☐	
Blinding of outcome assessments *Detection biases caused by the inadequate blinding of outcome assessments*	☐ ☐ ☐	
Incomplete outcome data *Attrition biases caused by the inadequate handling of incomplete outcome data*	☐ ☐ ☐	
Selective outcome reporting *Reporting biases caused by the selective reporting of outcomes*	☐ ☐ ☐	

D - Quality in Prognostic Studies (QUIPS)[30] (question 15)

Quality assessment - Quality in Prognostic Studies (QUIPS) tool				
Biases	**Issues to consider for judging overall rating of risk of bias**	**Study methods & comments**	**Rating of reporting**	**Rating of risk of bias**
Instructions to assess the risk of each potential bias:	*These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.*	*Provide comments or text excerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow*	*Yes, partial, no or unsure.*	*High, Moderate, or Low for 6 domains*
1. Study Participation	*Goal: To judge the risk of selection bias (likelihood that relationship between PF and outcome is different for participants and eligible non-participants).*			
Source of target population	The source population or population of interest is adequately described			
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)			
Recruitment period	Period of recruitment is adequately described			
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described			
Inclusion and exclusion criteria	Inclusion and exclusion criteria adequately described (e.g. including explicit diagnostic criteria or zero time description)			
Adequate study participation	There is adequate participation in the study by eligible individuals			
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described			
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			
2. Study Attrition	*Goal: To judge the risk of attrition bias (likelihood that relationship between PF and outcome are different for completing and non-completing participants).*			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.			
Attempts to collect information on participants	Attempts to collect information on participants who dropped out of the study are described.			

who dropped out				
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.			
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described There are no important differences between participants who completed the study and those who did not.			
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			
3. Prognostic Factor Measurement	*Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).*			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement)			
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall). Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.			
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.			
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.			
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data			
PF Measurement Summary	**PF is adequately measured in study participants to sufficiently limit potential bias.**			
4. Outcome Measurement	*Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).*			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.			

Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).			
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.			
Outcome Measurement Summary	Outcome of interest is adequately measured in study participants to sufficiently limit potential bias			
5. Study Confounding	*Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).*			
Important Confounders Measured	All important confounders, including treatments are measured.			
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).			
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall)			
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants			
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data			
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups) Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment)			
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome.**			
6. Statistical Analysis and Reporting	*Goal: To judge the risk of bias related to the statistical analysis and presentation of results*			

Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis			
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model. The selected statistical model is adequate for the design of the study			
Reporting of results	There is no selective reporting of results.			
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results**			

E – AMSTAS quality appraisal tool for systematic reviews[29]

AMSTAR – a measurement tool to assess the methodological quality of systematic reviews.

1. Was an 'a priori' design provided?
The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

- □ Yes
- □ No
- □ Can't answer
- □ Not applicable

---

2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

- □ Yes
- □ No
- □ Can't answer
- □ Not applicable

---

3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

- □ Yes
- □ No
- □ Can't answer
- □ Not applicable

---

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

- □ Yes
- □ No
- □ Can't answer
- □ Not applicable

---

5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."

- □ Yes
- □ No
- □ Can't answer
- □ Not applicable

---

6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

Note: Acceptable if not in table format as long as they are described as above.

- □ Yes
- □ No
- □ Can't answer
- □ Not applicable

---

7. Was the scientific quality of the included studies assessed and documented?

'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).

□ Yes
□ No
□ Can't answer
□ Not applicable

---

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.

□ Yes
□ No
□ Can't answer
□ Not applicable

---

9. Were the methods used to combine the findings of studies appropriate?

For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.

□ Yes
□ No
□ Can't answer
□ Not applicable

---

10. Was the likelihood of publication bias assessed?

An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

□ Yes
□ No
□ Can't answer
□ Not applicable

---

11. Was the conflict of interest included?

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

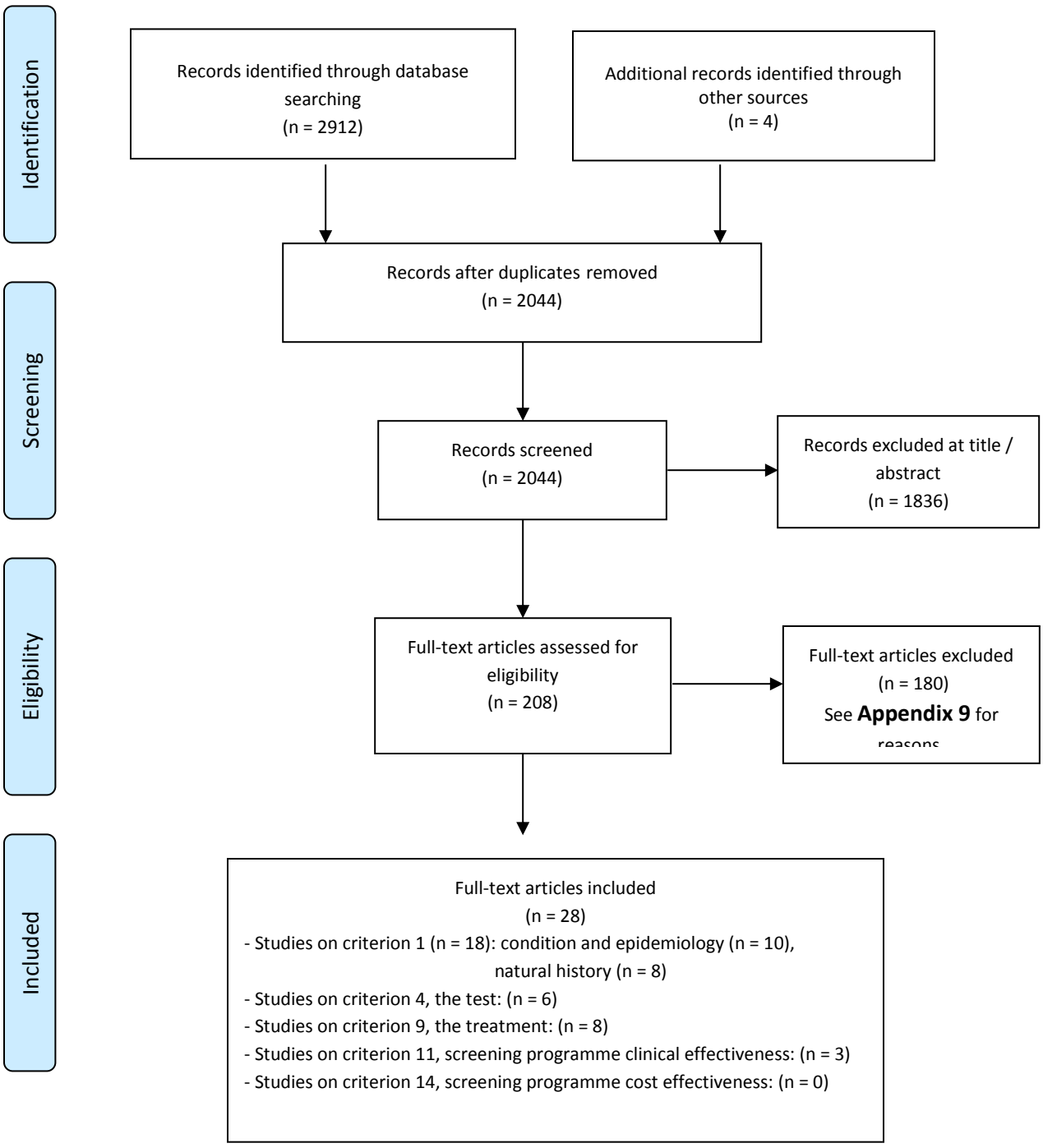
Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.

□ Yes
□ No
□ Can't answer
□ Not applicable

Shea *et al. BMC Medical Research Methodology* 2007 **7**:10 doi:10.1186/1471-2288-7-10

Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010.

Appendix 5. PRISMA Flow Diagram for rapid review (questions 1-14, 16-19, 21-22)



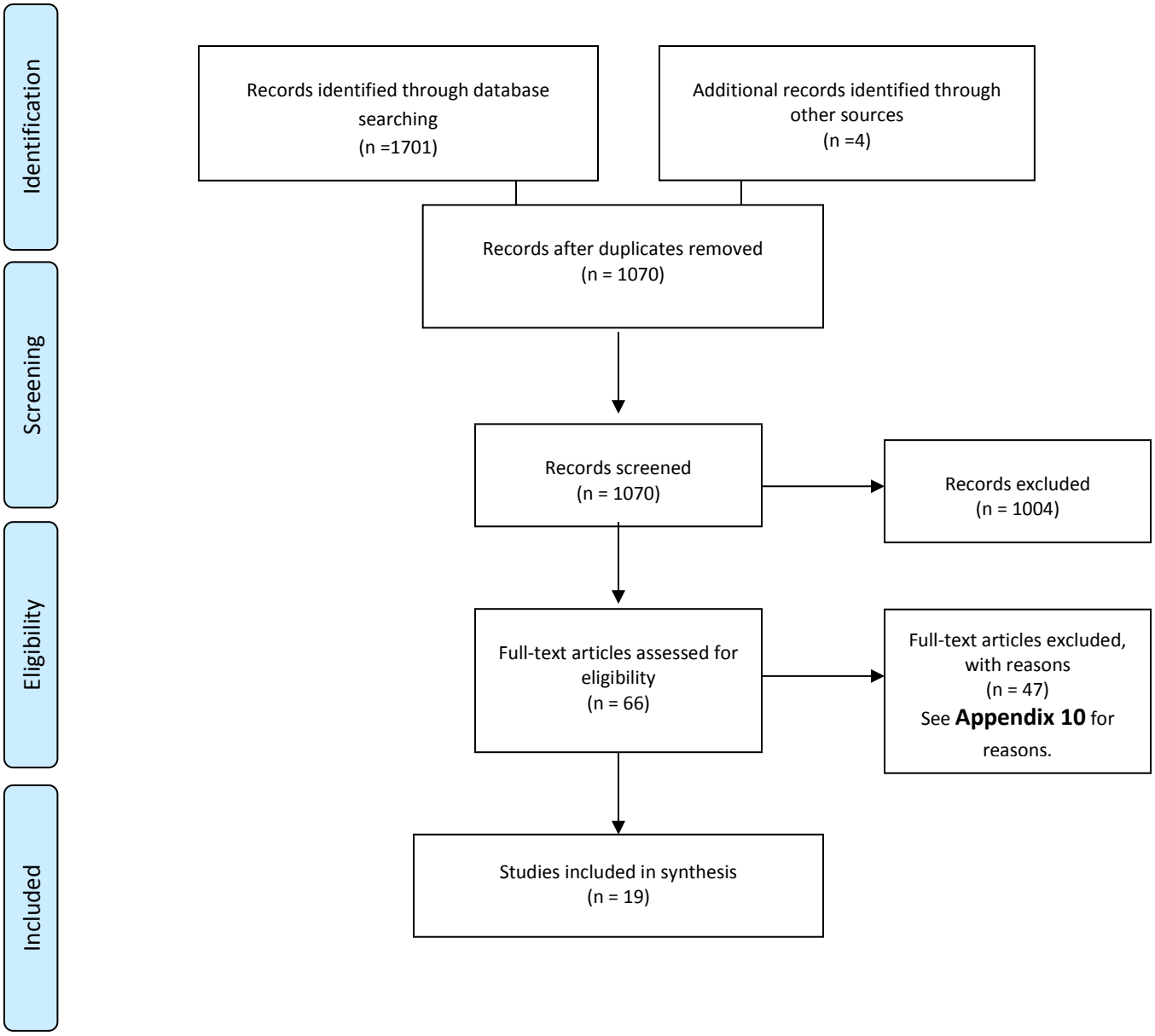
Appendix 6.Overview of included studies per UK NSC criterion and key question (1-14, 16-19, 21-22)

Study reference Author/ year / country	Information on epidemiology (criterion 1)										Information on natural history (criterion 1)				Information on test accuracy (criterion 4)			Information on IAP effectiveness (criterion 9)		Information on screening clinical effectiveness (criterion 11)	Information on screening cost effectiveness (criterion 14)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	16	17a	17b	18	19	21	22
Bauserman 2013[114] USA																				X	
Berardi 2013[40] Italy														X			X	X			
BPSU 2016[1,39,72]	X	X	X	X	X	X		X													
De Luca 2016[80] Italy																		X			
Eastwood 2015[46] Northern Ireland	X	X	X	X	X		X		X	X											
Ecker 2013[115] USA																				X	
El Helali 2012[83] France																		X	X		
Fairlie 2013[84] USA																		X			
Horvath 2013[116] Hungary																				X	
Kojima 2014[81] Japan																		X	X		
Kunze 2015[41] Germany												X			X	X					
Kwatra 2014[42] South Africa												X									
Lamagni 2013[19] UK	X					X															
Le Doare 2016[43] Gambia													X	X							
MacKay 2012[44] USA												X				X					
Manktelow 2016[38] Preliminary data UK				X					X	X											

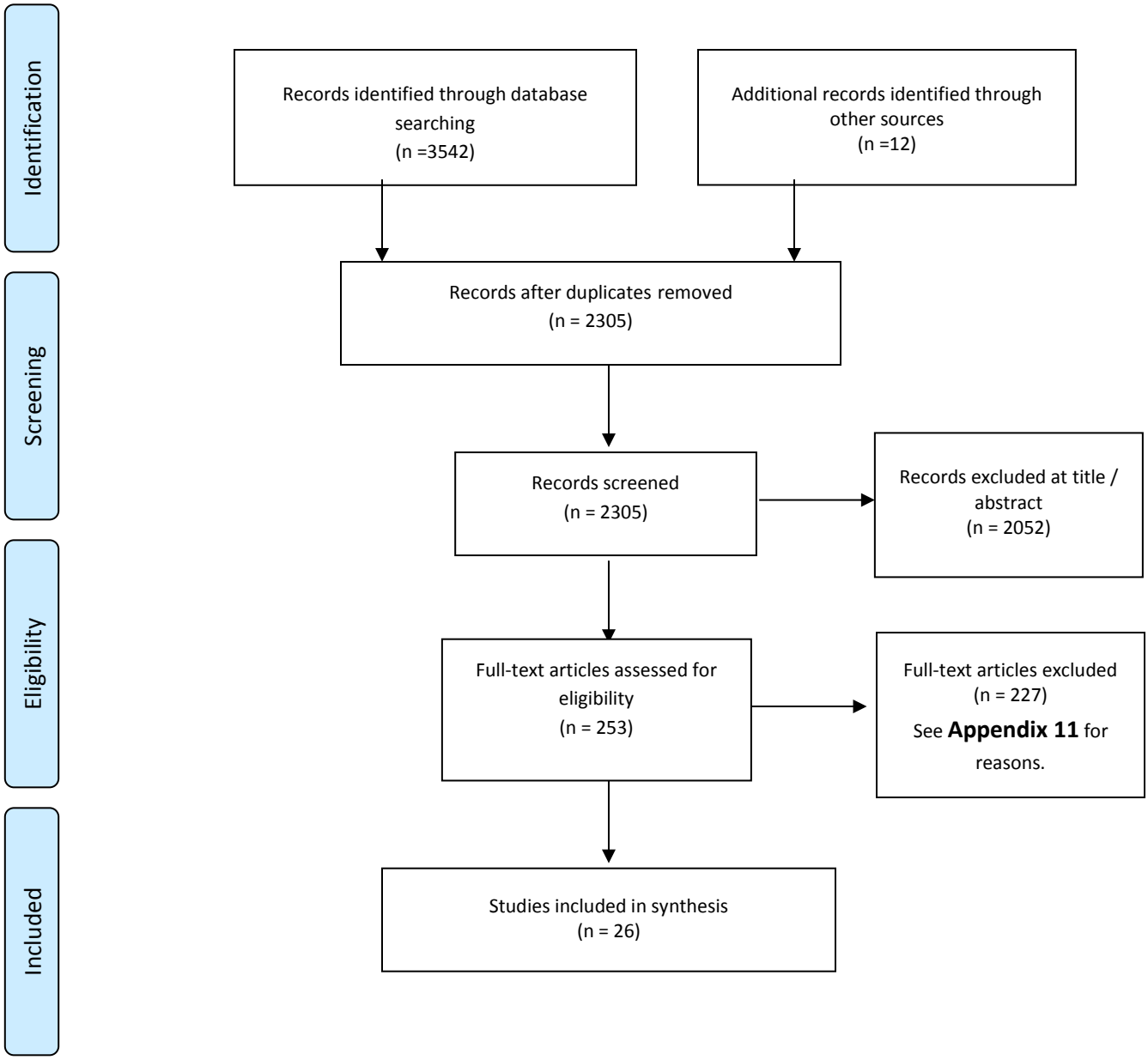
Study reference Author/ year / country	Information on epidemiology (criterion 1)										Information on natural history (criterion 1)				Information on test accuracy (criterion 4)			Information on IAP effectiveness (criterion 9)		Information on screening clinical effectiveness (criterion 11)	Information on screening cost effectiveness (criterion 14)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	16	17a	17b	18	19	21	22
Matsubara 2013[50] Japan							X	X													
Nan 2015[52] Systematic review									X												
Ohlsson 2014[85] Systematic review																		X	X		
Okike 2014[49] UK, Republic of Ireland	X																				
PHE 2014[36] England, Wales, Northern Ireland	X																				
PHE 2015[37] England, Wales, Northern Ireland	X																				
Scasso 2015[45] Uruguay												X				X					
Szymusik 2014[48] Poland												X			X	X					
Turrentine 2013[82] USA																		X			
Williams 2013[51] UK				X																	
Yeung 2014[47] Hong Kong														X							
Zuppa 2014[77] Italy																	X	X			
Total number of included studies	**6**	**2**	**2**	**4**	**2**	**2**	**2**	**2**	**3**	**2**	**0**	**5**	**1**	**3**	**2**	**4**	**2**	**8**	**3**	**3**	**0**

BPSU, British Paediatric Surveillance Unit; IAP, intrapartum antibiotic prophylaxis; PHE, Public Health England.

Appendix 7. PRISMA Flow Diagram for Question 15



Appendix 8. PRISMA Flow Diagram for Question 20



Appendix 9. List of studies that are not included in the rapid review (n=180)

A - Studies with high applicability concerns (n=11, 2 of which are included for another review question)

Reference	Applicability concern
1. Abdelazim, I. A. (2013). "Intrapartum polymerase chain reaction for detection of group B streptococcus colonisation." Australian and New Zealand Journal of Obstetrics and Gynaecology **53**(3): 236-242.	35-37 weeks and intrapartum, selective culture, but vaginal swabs only
2. Berardi, A., et al. (2014). "Factors associated with intrapartum transmission of group B Streptococcus." Pediatric Infectious Disease Journal **33**(12): 1211-1215.	Recto-vaginal swabs at 35-37 weeks, intrapartum vaginal swabs only, selective culture
3. Cutland, C. L., et al. (2012). "Maternal HIV infection and vertical transmission of pathogenic bacteria." Pediatrics **130**(3): e581-e590.	Vaginal swabs only
4. El Helali, N., et al. (2012). "Cost and effectiveness of intrapartum group B streptococcus polymerase chain reaction screening for term deliveries." Obstetrics and Gynecology **119**(4): 822-829.	Vaginal swabs only
5. Florindo, C., et al. (2014). "Accuracy of prenatal culture in predicting intrapartum group B streptococcus colonization status." 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 **27**(6): 640-642.	35-37 weeks, screening test unclear, methodological heterogeneity, recto-vaginal swabs on admission for delivery with selective culture
6. Hamedi, A., et al. (2012). "Evaluation of group B streptococci colonization rate in pregnant women and their newborn." Acta Medica Iranica **50**(12): 805-808.	Recto-vaginal swabs during labour, but nonselective culture
7. Kwatra, G., et al. (2014). "Serotype-specific acquisition and loss of group B streptococcus recto-vaginal colonization in late pregnancy." PLoS ONE **9**(6): e98778.	GBS screen was not intrapartum but at 37+ weeks and index test between 31-35 weeks; recto-vaginal swabs, selective culture (CHROMagar StrepB)
8. Poncelet-Jasserand, E., et al. (2013). "Reduction of the use of antimicrobial drugs following the rapid detection of Streptococcus agalactiae in the vagina at delivery by real-time PCR assay." BJOG: An International Journal of Obstetrics and Gynaecology **120**(9): 1098-1108.	34-38 weeks & intrapartum, vaginal swabs only, selective culture
9. Skret-Magierlo, J., et al. (2013). "Colonization with Group B streptococcus and Ureaplasma urealyticum among parturient women in Poland and Ukraine." International Journal of Gynecology and Obstetrics **120**(1): 95-96.	Vaginal swabs only
10. Tanaka, K., et al. (2016). "Intrapartum group B Streptococcus screening using real-time polymerase chain reaction in Japanese population." Journal of Maternal-Fetal and Neonatal Medicine **29**(1): 130-134.	35-37 weeks and before delivery/IAP plus comparison with rapid testing, recto-vaginal swabs, but nonselective culture
11. Yang, M. J., et al. (2012). "Prevalence of maternal group B streptococcus colonization and vertical transmission in low-risk women in a single institute." Journal of the Chinese Medical Association **75**(1): 25-28.	Vaginal swab only, nonselective culture

GBS, group B *Streptococcus*.

B - Excluded studies with reason (n=171)

Reference	Reason for exclusion
1. Adeniran, A. S., et al. (2015). "Role of Risk-Based Approach in the Prevention of Vertical Transmission of Neonatal Sepsis." Nigerian Postgraduate Medical Journal **22**(2): 88-92.	Risk-based approach, no transmission data
2. Alam, M. M., et al. (2014). "Neonatal sepsis following prolonged rupture of membranes in a tertiary care hospital in Karachi, Pakistan." Journal of Infection in Developing Countries **8**(1): 67-73.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
3. Albouy-Llaty, M., et al. (2012). "Improving perinatal Group B streptococcus screening with process indicators." Journal of Evaluation in Clinical Practice 18(4): 727-733.	Already included in October 2012 addendum of previous GBS review (Bazian 2012)
4. Al-Kadri, H. M., et al. (2013). "Maternal and neonatal risk factors for early-onset group B streptococcal disease: A case control study." International Journal of Women's Health **5**(1): 729-735.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
5. Allen, V. M., et al. (2012). "Management of group B streptococcal bacteriuria in pregnancy." Journal of Obstetrics & Gynaecology Canada: JOGC 34(5): 482-486.	Clinical practice guideline for GBS bacteriuria in pregnancy only
6. Alp, F., et al. (2016). "Screening and genotyping of group B streptococcus in pregnant and non-pregnant women in Turkey." Journal of Infection in Developing Countries 10(3): 222-226.	Screening test, only 1 time point
7. Al-Taiar, A., et al. (2013). "Neonatal infections in China, Malaysia, Hong Kong and Thailand." Archives of Disease in Childhood Fetal and neonatal edition. 98(3): F249-255.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
8. Alyamac Dandizdar, E., et al. (2012). "Group B streptococcus infection in neonatal intensive care unit." Turkiye Klinikleri Journal of Medical Sciences 32(3): 702-706.	Full-text in Turkish language
9. Baker, C. J., et al. (2014). "Maternal antibody at delivery protects neonates from early onset group B streptococcal disease." Journal of Infectious Diseases 209(5): 781-788.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
10. Ballard, M. S., et al. (2016). "The changing epidemiology of group B streptococcus bloodstream infection: a multi-national population-based assessment." Infectious Diseases 48(5): 386-391.	No EOGBS data for the UK reported
11. Barcaite, E., et al. (2012). "Group B streptococcus and Escherichia coli colonization in pregnant women and neonates in Lithuania." International Journal of Gynecology and Obstetrics 117(1): 69-73.	>10% received IAP
12. Bekker, V., et al. (2014). "Incidence of invasive group B streptococcal disease and pathogen genotype distribution in newborn babies in the Netherlands over 25 years: A nationwide surveillance study." The Lancet Infectious Diseases 14(11): 1083-1089.	Before and after introduction of risk-based approach and IAP in the Netherlands, outcomes of risk-based screening programme
13. Ben Hamouda, H., et al. (2013). "Clinical outcome and prognosis of neonatal bacterial meningitis." Archives de Pediatrie 20(9): 938-944.	Full-text in French language
14. Berardi, A., et al. (2015). "Safety of physical examination alone for managing well-appearing neonates >35 weeks gestation at risk for early-onset sepsis." Journal of Maternal-Fetal and Neonatal Medicine 28(10): 1123-1127.	>10% received IAP
15. Berardi, A., et al. (2013). "Impact of perinatal practices for early-onset group B streptococcal disease prevention." Pediatric Infectious Disease Journal 32(7): e265-e271.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data

Reference	Reason for exclusion
16. Berger, M. B., et al. (2012). "Early hospital discharge of infants born to group B streptococci-positive mothers: a decision analysis." BJOG: An International Journal of Obstetrics & Gynaecology 119(4): 439-448.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
17. Bizzarro, M. J., et al. (2015). "Neonatal sepsis 2004-2013: The rise and fall of coagulase-negative staphylococci." Journal of Pediatrics 166(5): 1193-1199.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
18. Brady, M. T. and R. A. Polin (2013). "Prevention and management of infants with suspected or proven neonatal sepsis." Pediatrics 132(1): 166-168.	Commentary
19. Brigtsen, A. K., et al. (2015). "Maternal colonization with group B streptococcus is associated with an increased rate of infants transferred to the neonatal intensive care unit." Neonatology 108(3): 157-163.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
20. Briody, V. A., et al. (2016). "Use of Cefazolin for Group B Streptococci Prophylaxis in Women Reporting a Penicillin Allergy Without Anaphylaxis." Obstetrics and Gynecology 127(3): 577-583.	Appropriate vs inappropriate IAP, no data on EOGBS
21. Bromiker, R., et al. (2013). "Correlation of bacterial type and antibiotic sensitivity with maternal antibiotic exposure in early-onset neonatal sepsis." Neonatology 103(1): 48-53.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
22. Brzychczy-Wloch, M., et al. (2013). "Incidence of maternal GBS colonization and neonatal GBS disease among very low birth weight Polish neonates." Medical Science Monitor 19: 34-39.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
23. Cantoni, L., et al. (2013). "Physical examination instead of laboratory tests for most infants born to mothers colonized with group B streptococcus: Support for the centers for disease control and prevention's 2010 recommendations." Journal of Pediatrics 163(2): 568-573.e561.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
24. Capan, M., et al. (2012). "Epidemiology and management of group B streptococcal colonization during pregnancy in Africa." Wiener Klinische Wochenschrift 124(3 SUPPL.): 14-16.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data, not a systematic review
25. Chan, G. J., et al. (2013). "Early-onset neonatal sepsis in Dhaka, Bangladesh: Risk associated with maternal bacterial colonisation and chorioamnionitis." Tropical Medicine and International Health 18(9): 1057-1064.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
26. Chan, G. J., et al. (2013). "Maternal and neonatal colonization in Bangladesh: Prevalences, etiologies and risk factors." Journal of Perinatology 33(12): 971-976.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
27. Chan, W. S. W., et al. (2014). "Rapid identification of group B streptococcus carriage by PCR to assist in the management of women with prelabour rupture of membranes in term pregnancy." Australian and New Zealand Journal of Obstetrics and Gynaecology 54(2): 138-145.	Rapid test vs. culture, only 1 timepoint, 0 EOGBS cases
28. Chhin, D., et al. (2013). "Relationship between cord blood vitamin D level and group B Streptococcus vaginal carriage rate in pregnant women." e-SPEN Journal 8(4): e150-e154.	Vertical transmission but only third trimester GBS screening, intrapartum sample only for preterm birth, only vaginal swab without selective culturing
29. Chu, S. M., et al. (2014). "Neurological complications after neonatal bacteremia: the clinical characteristics, risk factors, and outcomes." PLoS ONE 9(11): e105294.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data; not regional or national, only 1 hospital
30. Colicchia, L. C., et al. (2015). "Recurrence of group B streptococcus colonization in successive pregnancies." Journal of perinatology: official journal of the California Perinatal Association 35(3): 173-176.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data

Reference	Reason for exclusion
31. Crespo-Ortiz, M. D. P., et al. (2014). "Emerging trends in invasive and noninvasive isolates of Streptococcus agalactiae in a Latin American hospital: A 17-year study." BMC Infectious Diseases 14 (1) (no pagination)(428).	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
32. Creti, R., et al. (2013). "Characteristics of neonatal GBS disease during a multicentre study (2007-2010) and in the year 2012." Annali Dell'Istituto Superiore di Sanita 49(4): 370-375.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
33. Cutland, C. L., et al. (2015). "Increased risk for group b streptococcus sepsis in young infants exposed to hiv, soweto, south africa, 2004-20081." Emerging Infectious Diseases 21(4): 638-645.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
34. Dagnew, A. F., et al. (2012). "Variation in reported neonatal group B streptococcal disease incidence in developing countries." Clinical Infectious Diseases 55(1): 91-102.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
35. Dangor, Z., et al. (2015). "Correlates of protection of serotype-specific capsular antibody and invasive Group B Streptococcus disease in South African infants." Vaccine 33(48): 6793-6799.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
36. Dangor, Z., et al. (2015). "HIV-1 Is Associated with Lower Group B Streptococcus Capsular and Surface-Protein IgG Antibody Levels and Reduced Transplacental Antibody Transfer in Pregnant Women." Journal of Infectious Diseases 212(3): 453-462.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
37. Dangor, Z., et al. (2014). "Review on the association of Group B Streptococcus capsular antibody and protection against invasive disease in infants." Expert Review of Vaccines 14(1): 135-149.	Systematic review without GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
38. Dangor, Z., et al. (2015). "Burden of invasive group B Streptococcus disease and early neurological sequelae in South African infants." PLoS ONE 10 (4) (no pagination)(e0123014).	EOGBS and LOGBS data cannot be separated
39. Darlow, B. A., et al. (2016). "Early-onset neonatal group B streptococcus sepsis following national risk-based prevention guidelines." Australian and New Zealand Journal of Obstetrics and Gynaecology 56(1): 69-74.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
40. Di Renzo, G. C., et al. (2015). "Intrapartum GBS screening and antibiotic prophylaxis: A European consensus conference." Journal of Maternal-Fetal and Neonatal Medicine 28(7): 766-782.	Not a systematic review
41. Dickinson, P., et al. (2015). "Whole blood gene expression profiling of neonates with confirmed bacterial sepsis." Genomics Data 3: 41-48.	No results presented, no EOGBS data
42. Edmond, K. M., et al. (2012). "Group B streptococcal disease in infants aged younger than 3 months: Systematic review and meta-analysis." The Lancet 379(9815): 547-556.	Published January 2012 and included in previous GBS review by Bazian (2012)
43. Ergaz, Z., et al. (2013). "No change in antibiotic susceptibility patterns in the neonatal icu over two decades." Pediatric Critical Care Medicine 14(2): 164-170.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
44. Ferrieri, P., et al. (2013). "Serotype IV and invasive group B Streptococcus disease in neonates, Minnesota, USA, 2000-2010." Emerging Infectious Diseases 19(4): 551-558.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
45. Fiolo, K., et al. (2012). "Infection rate and streptococcus agalactiae serotypes in samples of infected neonates in the city of campinas (sao paulo), Brazil." Revista Brasileira de Ginecologia e Obstetricia 34(12): 544-549.	Full-text in Portuguese language

Reference	Reason for exclusion
46. Fjalstad, J. W., et al. (2016). "Early-onset Sepsis and Antibiotic Exposure in Term Infants: A Nationwide Population-based Study in Norway." Pediatric Infectious Disease Journal 35(1): 1-6.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
47. Flidel-Rimon, O., et al. (2012). "Limitations of the risk factor based approach in early neonatal sepsis evaluations." Acta Paediatrica, International Journal of Paediatrics 101(12): e540-e544.	Outside UK and no separate EOGBS data
48. Frigati, L., et al. (2014). "A retrospective review of group B streptococcal infection in the Metro East area of the Western Cape province: 2010 to 2011." Southern African Journal of Epidemiology and Infection 29(1): 33-36.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
49. Ganor-Paz, Y., et al. (2015). "Obstetric and neonatal outcomes after preterm premature rupture of membranes among women carrying group B streptococcus." International Journal of Gynecology and Obstetrics 129(1): 13-16.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
50. Ghaddar, N., et al. (2014). "Evaluation of chromogenic medium and direct latex agglutination test for detection of group B streptococcus in vaginal specimens from pregnant women in Lebanon and Kuwait." Journal of Medical Microbiology 63(Pt 10): 1395-1399.	Comparison of different screening tests but only 1 time point (35-37 weeks)
51. Giannoni, E., et al. (2016). "Incidence and Outcome of Group B Streptococcal Sepsis in Infants in Switzerland." Pediatric Infectious Disease Journal 35(2): 222-224.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
52. Ginsberg, G. M., et al. (2013). "Should Israel screen all mothers-to-be to prevent early-onset of neonatal group B streptococcal disease? A cost-utility analysis." Israel Journal of Health Policy Research 2 (1) (no pagination)(6).	Cost-utility analysis for Israel, outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
53. Glackin, S., et al. (2015). "A less invasive approach to screening for early onset neonatal GBS." Irish Medical Journal 108(3): 81-83.	Dublin, Republic of Ireland, only 1 hospital
54. Hadavand, S., et al. (2015). "Frequency of Group B Streptococcal Colonization in Pregnant Women Aged 35- 37 Weeks in Clinical Centers of Shahed University, Tehran, Iran." Iranian Journal of Pathology 10(2): 120-126.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
55. Hakansson, S., et al. (2014). "Real-time PCR-assay in the delivery suite for determination of group B streptococcal colonization in a setting with risk-based antibiotic prophylaxis." 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 27(4): 328-332.	IAP > 10%
56. Hayward, K., et al. (2012). "Perinatal exposures and kawasaki disease in Washington State: A population-based, case-control study." Pediatric Infectious Disease Journal 31(10): 1027-1031.	No EOGBS long-term morbidity data
57. Heath, P. T. and L. A. Jardine (2014). "Neonatal infections: group B streptococcus." Clinical Evidence.	Systematic review about early routine antibiotic prophylaxis vs. monitoring and selected treatment in asymptomatic newborns with known risk factors of EOGBS
58. Heidarzadeh Arani, M., et al. (2013). "Predictive value of interleukin-6 (IL6) in term neonates with early sepsis during 2010-2011." Jundishapur Journal of Microbiology 6 (10) (no pagination)(e8580).	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data

Reference	Reason for exclusion
59. Hon, K. L., et al. (2015). "Cardiopulmonary morbidity of streptococcal infections in a PICU." The clinical respiratory journal 9(1): 45-52.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
60. Hsieh, W. S., et al. (2014). "Epidemiology and Prevalence of Bloodstream Infections in a Regional Hospital in Northern Taiwan During 2008-2013." Journal of Experimental and Clinical Medicine (Taiwan) 6(6): 187-189.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
61. Hsu, J. F., et al. (2015). "Predictors of clinical and microbiological treatment failure in neonatal bloodstream infections." Clinical Microbiology and Infection 21(5): 482.e489-482.e417.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
62. Hudson, L. D., et al. (2013). "Long-term sequelae of childhood bacterial meningitis." Current Infectious Disease Reports 15(3): 236-241.	Not a systematic review and no separate data for EOGBS
63. Iqbal, Q., et al. (2013). "Thrombocytopenia and other hematological parameters in culture positive neonatal sepsis and their impact." Journal of Pediatric Infectious Diseases 8(1): 25-29.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
64. Ireland, S., et al. (2014). "Group B Streptococcal infection in the first 90 days of life in North Queensland." Australian and New Zealand Journal of Obstetrics and Gynaecology 54(2): 146-151.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
65. Irwin, A. D., et al. (2015). "Etiology of childhood bacteremia and timely antibiotics administration in the emergency department." Pediatrics 135(4): 635-642.	No EOGBS data, 1 children's emergency department in the UK
66. Jah, C. (2014). "GBS updates from a homebirth perspective." Midwifery Today with International Midwife(110): 49-54.	Not a systematic review
67. Jipa, R., et al. (2013). "Current guidelines recommendations for management of group B streptococcal infections in pregnant women." Gineco.eu 9(3): 141-146.	Not a systematic review and no original data
68. Joao, E., et al. (2013). "Institutional prevention policies and rates of Group B Streptococcus infection among HIV-infected pregnant women and their infants in Latin America." International Journal of Gynecology and Obstetrics 120(2): 144-147.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data, no EOGBS cases for predictive value calculation
69. Johri, A. K., et al. (2013). "Epidemiology of group B Streptococcus in developing countries." Vaccine 31(S4): D43-D45.	Not a systematic review
70. Joubrel, C., et al. (2014). "Comparative evaluation of 5 different selective media for Group B Streptococcus screening in pregnant women." Diagnostic Microbiology and Infectious Disease 80(4): 282-284.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data; different GBS screening methods compared to gold standard, only 1 time point
71. Joubrel, C., et al. (2015). "Group B streptococcus neonatal invasive infections, France 2007-2012." Clinical Microbiology and Infection 21(10): 910-916.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
72. Kabiri, D., et al. (2015). "Antepartum membrane stripping in GBS carriers, is it safe? (The STRIP-G study)." PLoS ONE 10 (12) (no pagination)(e0145905).	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
73. Kalin, A., et al. (2015). "Severe sepsis in women with group B Streptococcus in pregnancy: An exploratory UK national case-control study." BMJ Open 5 (10) (no pagination)(e007976).	Maternal GBS sepsis with information on the causative organisms of infant sepsis not available
74. Kessous, R., et al. (2012). "Bacteruria with group-B streptococcus: Is it a risk factor for adverse pregnancy outcomes." Journal of Maternal-Fetal and Neonatal Medicine 25(10): 1983-1986.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data

Reference	Reason for exclusion
75. Kiwanuka, J., et al. (2013). "The Microbial Spectrum of Neonatal Sepsis in Uganda: Recovery of Culturable Bacteria in Mother-Infant Pairs." PLoS ONE 8 (8) (no pagination)(e72775).	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
76. Kleweis, S. M., et al. (2015). "Maternal obesity and rectovaginal group B streptococcus colonization at term." Infectious Diseases in Obstetrics and Gynecology 2015 (no pagination)(586767).	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
77. Knowles, S. J., et al. (2014). "Maternal sepsis incidence, aetiology and outcome for mother and fetus: A prospective study." BJOG: An International Journal of Obstetrics and Gynaecology 122(5): 663-671.	Maternal sepsis in Ireland, no GBS carriage or EOGBS data
78. Ko, D. W. H., et al. (2015). "Group B streptococcal disease and genotypes in Australian infants." Journal of Paediatrics and Child Health 51(8): 808-814.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
79. Kolkman, D. G., et al. (2013). "Implementation of a cost-effective strategy to prevent neonatal early-onset group B haemolytic streptococcus disease in the Netherlands." BMC Pregnancy & Childbirth 13: 155.	Study protocol without results data
80. Konikkara, K. P., et al. (2013). "Comparison of various culture methods for isolation of group B streptococcus from intrapartum vaginal colonization." Journal of Laboratory Physicians 5(1): 42-45.	Comparison of 3 different GBS screening methods at 1 time point, no transition or transmission data
81. Koumans, E. H. A., et al. (2012). "Prevention of mother-to-child transmission of infections during pregnancy: Implementation of recommended interventions, United States, 2003-2004." American Journal of Obstetrics and Gynecology 206(2): 158.e151-158.e111.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
82. Kwatra, G., et al. (2015). "Natural acquired humoral immunity against serotype-specific group B Streptococcus rectovaginal colonization acquisition in pregnant women." Clinical Microbiology and Infection 21(6): 568.e513-568.e562.	Dynamics of GBS colonisation already published by Kwatra et al 2014 and included, no transition or predictive value data in this article
83. Lacaze-Masmonteil, T., et al. (2014). "Value of a single C-reactive protein measurement at 18 h of age." Archives of Disease in Childhood: Fetal and Neonatal Edition 99(1): F76-F79.	No separate data for EOGBS
84. Law, K. S., et al. (2013). "A comparative study assessing the efficacy and acceptability of anorectal swabs for antenatal GBS screening." Journal of Medical Screening 20(1): 46-48.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
85. Lee, B., et al. (2016). "Reductions in neonatal listeriosis: "Collateral benefit" of Group B streptococcal prophylaxis?" Journal of Infection 72(3): 317-323.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
86. Libster, R., et al. (2012). "Long-term outcomes of group B streptococcal meningitis." Pediatrics 130(1): e8-e15.	No separate EOGBS data and not regional or national coverage
87. Lin, C. B., et al. (2012). "Very low birth weight neonates who survive early-onset sepsis do not have an increased risk of developing late-onset sepsis." Early Human Development 88(11): 905-909.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
88. Lin, M. C., et al. (2012). "Factors for poor prognosis of neonatal bacterial meningitis in a medical center in Northern Taiwan." Journal of Microbiology, Immunology and Infection 45(6): 442-447.	No separate data for EOGBS longterm morbidity and not regional or national coverage
89. Lin, M. C., et al. (2015). "Evolving trends of neonatal and childhood bacterial meningitis in northern Taiwan." Journal of Microbiology, Immunology and Infection 48(3): 296-301.	No EOGBS data
90. Lito, D., et al. (2013). "TORCH serology and group B Streptococcus screening analysis in the population of a maternity." Acta Medica Portuguesa 26(5): 549-554.	Full-text in Portuguese language

Reference	Reason for exclusion
91. Liu, H., et al. (2015). "Estimating the burden of invasive Group B Streptococcal disease in young infants in southern mainland China: An observational study." International journal of clinical and experimental medicine 8(8): 13699-13707.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
92. Logan, L. K., et al. (2013). "A prospective cohort pilot study of the clinical and molecular epidemiology of Staphylococcus aureus in pregnant women at the time of group B streptococcal screening in a large urban medical center in Chicago, IL USA." Virulence 4(7): 654-658.	Not about GBS carriage or EOGBS
93. Lukacs, S. L. and S. J. Schrag (2012). "Clinical sepsis in neonates and young infants, United States, 1988-2006.[Erratum appears in J Pediatr. 2012 Sep;161(3):573]." Journal of Pediatrics 160(6): 960-965.e961.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
94. Luthander, J., et al. (2013). "Age and risk factors influence the microbial aetiology of bloodstream infection in children." Acta Paediatrica, International Journal of Paediatrics 102(2): 182-186.	No separate data for EOGBS
95. Luthander, J., et al. (2015). "The aetiology of paediatric bloodstream infections changes after pneumococcal vaccination and group B streptococcus prophylaxis." Acta Paediatrica, International Journal of Paediatrics 104(9): 933-939.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data; risk-based IAP
96. Maamouri, G. A., et al. (2013). "Investigating the rate of group B streptococcus in below 3 months year old infants with sepsis clinical symptoms hospitalized in Ghaem Hospital of Mashahd." Iranian Journal of Neonatology 4(1): 12-16.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
97. Mitha, A., et al. (2013). "Neonatal infection and 5-year neurodevelopmental outcome of very preterm infants." Pediatrics 132(2): e372-e380.	No separate data for EOGBS
98. Miyata, A., et al. (2012). "Early-onset group B streptococcal disease following culture-based screening in Japan: A single center study." Journal of Obstetrics and Gynaecology Research 38(8): 1052-1056.	IAP > 10%
99. Monari, F., et al. (2013). "Fetal bacterial infections in antepartum stillbirth: A case series." Early Human Development 89(12): 1049-1054.	Outside UK and stillbirth data
100. Money, D. and V. M. Allen (2013). "The prevention of early-onset neonatal group B streptococcal disease." Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 35(10): 939-951.	Updated clinical practice guideline
101. Moorthy, V., et al. (2014). "Effective identification and management of Group B Streptococcus in Pregnancy and Labour." Archives of Disease in Childhood: Fetal and Neonatal Edition 99: A117-A121.	Conference abstract
102. Morozumi, M., et al. (2015). "Direct identification of Streptococcus agalactiae and capsular type by real-time PCR in vaginal swabs from pregnant women." Journal of Infection and Chemotherapy 21(1): 34-38.	Rapid vs. culture GBS screening test at 1 timepoint only
103. Mukhopadhyay, S., et al. (2014). "2010 Perinatal GBS prevention guideline and resource utilization." Pediatrics 133(2): 196-203.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
104. Mukhopadhyay, S., et al. (2013). "Neonatal early-onset sepsis evaluations among well-appearing infants: Projected impact of changes in CDC GBS guidelines." Journal of Perinatology 33(3): 198-205.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data

Reference	Reason for exclusion
105. Mukhopadhyay, S. and K. M. Puopolo (2012). "Risk Assessment in Neonatal Early Onset Sepsis." Seminars in Perinatology 36(6): 408-415.	Not a systematic review
106. Musilova, I., et al. (2016). "Streptococcus agalactiae in pregnancies complicated by preterm prelabor rupture of membranes." Journal of Maternal-Fetal and Neonatal Medicine 29(7): 1036-1040.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
107. Nair, I. S. (2014). "Prevention of early-onset group B streptococcal disease in newborns." Perinatology 14(4): 137-143.	Not a systematic review
108. Narava, S., et al. (2014). "Prevention of perinatal group B streptococcal infections: A review with an Indian perspective." Indian Journal of Medical Microbiology 32(1): 6-12.	Not a systematic review
109. Oh, W. (2013). "Early onset neonatal group B streptococcal sepsis." American Journal of Perinatology 30(2): 143-147.	Not a systematic review
110. O'Higgins, A. C., et al. (2014). "A clinical review of maternal bacteremia." International Journal of Gynecology and Obstetrics 124(3): 226-229.	Maternal bacteraemina in Ireland, no maternal GSB carriage or EOGBS data
111. Ohlsson, A., et al. (2014) Vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection. Cochrane Database of Systematic Reviews DOI: 10.1002/14651858.CD003520.pub3	No vertical transmission rates for women without intervention given
112. Ohlsson, A. and V. S. Shah (2013). "Intrapartum antibiotics for known maternal Group B streptococcal colonization." Cochrane database of systematic reviews (Online) 1: CD007467.	Duplicate
113. Okike, I. O., et al. (2014). "Trends in bacterial, mycobacterial, and fungal meningitis in England and Wales 2004-11: An observational study." The Lancet Infectious Diseases 14(4): 301-307.	No EOGBS data
114. Oncel, M. Y., et al. (2013). "The association of a cervical length of <25 mm in high-risk pregnancies on neonatal morbidity and mortality in preterm infants." Archives of Gynecology and Obstetrics 287(5): 893-899.	Outside UK, preterm babies, no separate data for GBS/EOGBS
115. Oncel, M. Y., et al. (2015). "Effect of maternal cervical bacterial colonization on neonatal outcome in high-risk pregnancies: Results from a tertiary maternity center in Turkey." Clinical and Experimental Obstetrics and Gynecology 42(4): 485-489.	IAP > 10%
116. Ozkan, H., et al. (2014). "Culture-proven neonatal sepsis in preterm infants in a neonatal intensive care unit over a 7 year period: Coagulase-negative Staphylococcus as the predominant pathogen." Pediatrics International 56(1): 60-66.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
117. Page-Ramsey, S. M., et al. (2013). "Prevalence of group B streptococcus colonization in subsequent pregnancies of group B streptococcus-colonized versus noncolonized women." American Journal of Perinatology 30(5): 383-388.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
118. Parks, T., et al. (2015). "Invasive streptococcal disease: A review for clinicians." British Medical Bulletin 115(1): 77-89.	Not a systematic review
119. Patel, A. L., et al. (2013). "Impact of early human milk on sepsis and health-care costs in very low birth weight infants." Journal of Perinatology 33(7): 514-519.	Not EOGBS

Reference	Reason for exclusion
120. Persaud, R. R., et al. (2015). "Perinatal antibiotic exposure of neonates in Canada and associated risk factors: A population-based study." Journal of Maternal-Fetal and Neonatal Medicine 28(10): 1190-1195.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
121. Petersen, K. B., et al. (2014). "Increasing prevalence of group B streptococcal infection among pregnant women." Danish Medical Journal 61(9): A4908.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data; urine and/or vaginal swabs, unclear when tested, no intrapartum testing
122. Picone, S., et al. (2014). "Infection in late preterm infants." Early Human Development 90(SUPPL.1): S71-S74.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
123. Polin, R. A., et al. (2012). "Management of Neonates with Suspected or Proven Early-Onset Bacterial Sepsis." Pediatrics 129(5): 1006-1015.	Not a systematic review
124. Porta, K. and D. Rizzolo (2015). "Preventing group B streptococcal infections in newborns." JAAPA 28(3): 24-29.	Not a systematic review
125. Puccio, G., et al. (2014). "Epidemiology of Toxoplasma and CMV serology and of GBS colonization in pregnancy and neonatal outcome in a Sicilian population." Italian Journal of Pediatrics 40 (1) (no pagination)(23).	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data; no cases of EOGBS in GBS screened women
126. Quan, V., et al. (2016). "Invasive Group B Streptococcal Disease in South Africa: Importance of Surveillance Methodology." PLoS ONE [Electronic Resource] 11(4): e0152524.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
127. Reuter, S., et al. (2014). "Respiratory distress in the newborn." Pediatrics in Review 35(10): 417-428; quiz 429.	Case reports
128. Richtmann, R., et al. (2012). "Evaluation of a strategy to prevent early neonatal group B streptococcus infection: A prospective cohort study." Journal of Pediatric Infectious Diseases 7(4): 145-149.	IAP > 10%
129. Rivera, L., et al. (2015). "Incidence and serotype distribution of invasive group B streptococcal disease in young infants: a multi-country observational study." BMC Pediatrics 15: 143.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
130. Robert Lee, S. Y. and C. W. Leung (2012). "Histological chorioamnionitis - Implication for bacterial colonization, laboratory markers of infection, and early onset sepsis in very-low-birth-weight neonates." Journal of Maternal-Fetal and Neonatal Medicine 25(4): 364-368.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data; no GBS screening in pregnant or intrapartum women performed, IAP in 49% of cases
131. Rodriguez-Granger, J., et al. (2012). "Prevention of group B streptococcal neonatal disease revisited. the DEVANI European project." European Journal of Clinical Microbiology and Infectious Diseases 31(9): 2097-2104.	Not a systematic review
132. Sadarangani, M., et al. (2015). "Childhood meningitis in the conjugate vaccine era: A prospective cohort study." Archives of Disease in Childhood 100(3): 292-294.	No separate data for EOGBS
133. Sakata, H. (2012). "Evaluation of intrapartum antibiotic prophylaxis for the prevention of early-onset group B streptococcal infection." Journal of Infection and Chemotherapy 18(6): 853-857.	IAP >10%; only 1 hospital
134. Sakata, H. (2014). "Pediatric invasive streptococcal infection in northern and eastern regions of Hokkaido, Japan from 2010 to 2012." Pediatrics International 56(3): 360-363.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data

Reference	Reason for exclusion
135. Schrag, S. J. and J. R. Verani (2013). "Intrapartum antibiotic prophylaxis for the prevention of perinatal group B streptococcal disease: Experience in the United States and implications for a potential group B streptococcal vaccine." Vaccine 31(S4): D20-D26.	Not a systematic review
136. Shah, D., et al. (2014). "Prospective analysis of risk factors associated with group B streptococcal colonisation in neonates born at a tertiary care centre in India." Paediatrics and International Child Health 34(3): 184-188.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data; only GBS colonisation data for the neonates, not the mothers, no EOGBS data
137. Shane, A. L. and B. J. Stoll (2014). "Neonatal sepsis: progress towards improved outcomes." Journal of Infection 68 Suppl 1: S24-32.	Not a systematic review
138. Shinjoh, M., et al. (2014). "Recent trends in pediatric bacterial meningitis in Japan--a country where Haemophilus influenzae type b and Streptococcus pneumoniae conjugated vaccines have just been introduced." Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy 20(8): 477-483.	No EOGBS data
139. Shirazi, M., et al. (2014). "The prevalence of group B Streptococcus colonization in iranian pregnant women and its subsequent outcome." International Journal of Fertility and Sterility 7(4): 267-270.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data; index test at 35-37 weeks culture from vaginal swabs only, no intrapartum GBS screening, outcome symptomatic neonatal sepsis
140. Shore, E. M. and M. H. Yudin (2012). "Choice of antibiotic for group B streptococcus in women in labour based on antibiotic sensitivity testing." Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 34(3): 230-235.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
141. Singer, H. S., et al. (2012). "Moving from PANDAS to CANS." Journal of Pediatrics 160(5): 725-731.	No long-term EOGBS morbidity data
142. Smith, A., et al. (2015). "Is Preterm Premature Rupture of Membranes Latency Influenced by Single Versus Multiple Agent Antibiotic Prophylaxis in Group B Streptococcus Positive Women Delivering Preterm?" Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 37(9): 777-783.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
143. Snaebjarnardottir, K., et al. (2013). "Bacterial meningitis in children in Iceland, 1975-2010: A nationwide epidemiological study." Scandinavian Journal of Infectious Diseases 45(11): 819-824.	No EOGBS data
144. Sridhar, S., et al. (2014). "Group B streptococcal infection in a tertiary hospital in India-1998-2010." Pediatric Infectious Disease Journal 33(10): 1091-1092.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data; India, EOGBS incidence before & after introduction of risk-based approach and IAP
145. Stafford, I. A., et al. (2012). "Efficacy of maternal and neonatal chemoprophylaxis for early-onset group B streptococcal disease." Obstetrics and Gynecology 120(1): 123-129.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
146. Steer, P. J. (2015). "FOR: the case for screening." BJOG : an international journal of obstetrics and gynaecology 122(3): 369.	Commentary
147. Stroustrup, A., et al. (2013). "Group B streptococcus exposure and self-limited respiratory distress in late preterm and term neonates." Neonatology 104(3): 210-215.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data

Reference	Reason for exclusion
148. Tajik, P., 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, 1263-1272; discussion 1273 DOI: 10.1111/1471-0528.12889	Preterm labour only
149. Tam, T., et al. (2012). "Recolonization of group B Streptococcus (GBS) in women with prior GBS genital colonization in pregnancy." Journal of Maternal-Fetal and Neonatal Medicine 25(10): 1987-1989	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
150. Taylor, J. A. and D. J. Opel (2012). "Choriophobia: A 1-act play." Pediatrics 130(2): 342-346.	Kind of case report
151. Tevdorashvili, G., et al. (2015). "Prevention and treatment strategy in pregnant women with group B streptococcal infection." Georgian Medical News(241): 15-23.	Not a systematic review
152. Ting, Y. T., et al. (2015). "Epidemiology of community-acquired bacteremia among infants in a medical center in Taiwan, 2002-2011." Journal of Microbiology, Immunology and Infection 48(4): 413-418.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
153. Todorova-Christova, M., et al. (2014). "A study on early-onset neonatal group B streptococcal infection, Bulgaria, 2007-2011." Archives de Pediatrie 21(9): 953-960.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
154. Tsai, C. H., et al. (2012). "Characteristics of early-onset neonatal sepsis caused by Escherichia coli." Taiwanese Journal of Obstetrics & Gynecology 51(1): 26-30.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
155. Tsai, M. H., et al. (2014). "Polymicrobial bloodstream infection in neonates: Microbiology, clinical characteristics, and risk factors." PLoS ONE 9 (1) (no pagination)(e83082).	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
156. Tsai, M. H., et al. (2015). "Breakthrough bacteremia in the neonatal intensive care unit: Incidence, risk factors, and attributable mortality." American Journal of Infection Control 43(1): 20-25.	Late-onset bloodstream infections, not EOGBS
157. Tudela, C. M., et al. (2012). "Intrapartum evidence of early-onset group B streptococcus." Obstetrics and Gynecology 119(3): 626-629.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
158. Turner, C., et al. (2012). "Group B streptococcal carriage, serotype distribution and antibiotic susceptibilities in pregnant women at the time of delivery in a refugee population on the Thai-Myanmar border." BMC Infectious Diseases 12 (no pagination)(34).	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
159. Turrentine, M. A., et al. (2016). "Efficiency of Screening for the Recurrence of Antenatal Group B Streptococcus Colonization in a Subsequent Pregnancy: A Systematic Review and Meta-analysis with Independent Patient Data." American Journal of Perinatology 33(5): 510-517.	Systematic review without GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
160. Van Der Ham, D. P., et al. (2014). "Can neonatal sepsis be predicted in late preterm premature rupture of membranes? Development of a prediction model." European Journal of Obstetrics Gynecology and Reproductive Biology 176(1): 90-95.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data; preterm birth
161. Venkatnarayan, K., et al. (2014). "Neonatal sepsis: A profile of a changing spectrum." Journal of Nepal Paediatric Society 34(3): 207-214.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
162. Verani, J. R., et al. (2014). "Early-onset group B streptococcal disease in the United States: Potential for further reduction." Obstetrics and Gynecology 123(4): 828-837.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data

Reference	Reason for exclusion
163. Villanueva-Uy, M. E., et al. (2015). "The Burden of Invasive Neonatal Group B Streptococcal (Gbs) Disease in Thailand and the Philippines." Southeast Asian Journal of Tropical Medicine & Public Health 46(4): 728-737.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data; Philippines and Thailand, risk-based approach, EOGBS incidence only
164. Wang, X., et al. (2013). "Comparative Microbial Analysis of Paired Amniotic Fluid and Cord Blood from Pregnancies Complicated by Preterm Birth and Early-Onset Neonatal Sepsis." PLoS ONE 8 (2) (no pagination)(e56131).	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
165. Wee, L. Y. J., et al. (2016). "A 15-year retrospective analysis of prognostic factors in childhood bacterial meningitis." Acta Paediatrica, International Journal of Paediatrics 105(1): e22-e29.	No separate data for EOGBS
166. Wojkowska-Mach, J., et al. (2012). "Early-onset infections of very-low-birth-weight infants in Polish neonatal intensive care units." Pediatric Infectious Disease Journal 31(7): 691-695.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data; preterm neonates only
167. Wortham, J. M., et al. (2016) Chorioamnionitis and culture-confirmed, early-onset neonatal infections. Pediatrics 137, DOI: 10.1542/peds.2015-2323	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
168. Yeung, S. W., et al. (2015). "Evaluation of an in-house real-time polymerase chain reaction method to identify group B streptococcus colonization in pregnancy." Journal of Obstetrics and Gynaecology Research 41(9): 1357-1362.	Rapid vs. culture screening test with 1 time point only
169. Zhang, J., et al. (2015). "Invasive group B streptococcal infection in infants in Shenzhen, China." International journal of clinical and experimental medicine 8(2): 2939-2943.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data
170. Zilberman, D., et al. (2014). "Does genital tract GBS colonization affect the latency period in patients with preterm premature rupture of membranes not in labor prior to 34 weeks?" 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 27(4): 338-341.	Outside UK and no GBS morbidity/transition/transmission/screening test/IAP/GBS screening programme data; recto-vaginal swab on admisson for PPROM at 23-34 weeks, selective culture, antibiotics in 58/60 GBS+, no EOGBS data
171. Zoysa, A., et al. (2012) Non-culture detection of Streptococcus agalactiae (Lancefield group BStreptococcus) in clinical samples by real-time PCR. Journal of Medical Microbiology 61, 1086-1090	Rapid method for GBS detection compared to culture from clinical samples, diagnosis not screening

EOGBS, early-onset group B *Streptococcus* disease; GBS, group B *Streptococcus*; IAP, intrapartum antibiotic prophylaxis; LOGBS, late-onset neonatal group B streptococcus disease; PPROM, preterm prelabour rupture of membranes.

Appendix 10. List of studies excluded from the systematic review for question 15 (n=47), with reason

Reference	Reason for exclusion
1. Almeida A, Villain A, Joubrel C, et al. Whole-Genome Comparison Uncovers Genomic Mutations between Group B Streptococci Sampled from Infected Newborns and Their Mothers. Journal of Bacteriology 2015; **197**(20): 3354-66.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
2. Ayoub EM, Swingle H. Pathogenic mechanisms in neonatal GBS infection. Antibiot Chemother 1985; **35**: 128-41.	Review
3. Berardi A, Rossi C, Creti R, et al. Group B Streptococcal Colonization in 160 Mother-Baby Pairs: A Prospective Cohort Study. Journal of Pediatrics 2013; 163(4): 1099-+.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
4. Berardi A, Rossi C, Guidotti I, et al. Factors associated with intrapartum transmission of group B Streptococcus. Pediatric Infectious Disease Journal 2014; 33(12): 1211-5.	Unable to distinguish data from those who received IAP and those who did not
5. Berner R, Bender A, Rensing C, Forster J, Brandis M. Low prevalence of the immunoglobulin-A-binding beta antigen of the C protein among Streptococcus agalactiae isolates causing neonatal sepsis.[Erratum appears in Eur J Clin Microbiol Infect Dis 2000 Jan;19(1):75]. Eur J Clin Microbiol Infect Dis. 1999;18(8):545-50.	Unable to distinguish data from those who received IAP and those who did not
6. Bidet P, Brahimi N, Chalas C, Aujard Y, Bingen E. Molecular characterization of serotype III group B-streptococcus isolates causing neonatal meningitis. Journal of Infectious Diseases 2003; 188(8): 1132-7.	Unable to distinguish data from early-onset cases to other cases
7. Bisharat N, Jones N, Marchaim D, et al. Population structure of group B streptococcus from a low-incidence region for invasive neonatal disease. Microbiology-(UK) 2005; 151: 1875-81.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
8. Brigtsen AK, Jacobsen AF, Dedi L, Melby KK, Fugelseth D, Whitelaw A. Maternal Colonization with Group B Streptococcus Is Associated with an Increased Rate of Infants Transferred to the Neonatal Intensive Care Unit. Neonatology 2015; 108(3): 157-63.	Not on transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease) and no bacterial load factor or bacterial molecular marker
9. Chan GJ, Modak JK, Mahmud AA, Baqui AH, Black RE, Saha SK. Maternal and neonatal colonization in Bangladesh: prevalences, etiologies and risk factors. Journal of Perinatology 2013; 33(12): 971-6.	No bacterial load factor or bacterial molecular marker
10. Chatellier S, Huet H, Kenzi S, Rosenau A, Geslin P, Quentin R. Genetic diversity of rRNA operons of unrelated Streptococcus agalactiae strains isolated from cerebrospinal fluid of neonates suffering from meningitis. Journal of Clinical Microbiology 1996; 34(11): 2741-7.	More than 10% of the participants had late-onset GBS
11. Chatellier S, Ramanantsoa C, Harriau P, Rolland K, Rosenau A, Quentin R. Characterization of Streptococcus agalactiae strains by randomly amplified polymorphic DNA analysis. Journal of Clinical Microbiology 1997; 35(10): 2573-9.	More than 10% of the participants had late-onset GBS
12. Chaudhry BY, Akhtar N, Balouch AH. Vaginal carriage rate of group B Streptococcus in pregnant women and its transmission to neonates. J Ayub Med Coll Abbottabad 2010; 22(4): 167-70.	No bacterial load factor or bacterial molecular marker
13. D'Urzo N, Martinelli M, Pezzicoli A, et al. Acidic pH Strongly Enhances In Vitro Biofilm Formation by a Subset of Hypervirulent ST-17 Streptococcus agalactiae Strains. Applied and Environmental Microbiology 2014; 80(7): 2176-85.	Unable to distinguish data from early-onset cases to other cases

Reference	Reason for exclusion
14. Davies HD, Jones N, Whittam TS, Elsayed S, Bisharat N, Baker CJ. Multilocus sequence typing of serotype III group B streptococcus and correlation with pathogenic potential. Journal of Infectious Diseases 2004; 189(6): 1097-102.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
15. De Francesco MA, Gargiulo F, Negrini R, Gelmi M, Manca N. Different sequence strains of Streptococcus agalactiae elicit various levels of cytokine production. Immunol Invest 2008; 37(8): 741-51.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
16. Dore N, Bennett D, Kaliszer M, Cafferkey M, Smyth CJ. Molecular epidemiology of group B streptococci in Ireland: associations between serotype, invasive status and presence of genes encoding putative virulence factors. Epidemiology and Infection 2003; 131(2): 823-33.	Unable to distinguish data from early-onset GBS cases to others
17. Eskandarian N, Ismail Z, Neela V, van Belkum A, Desa MN, Amin Nordin S. Antimicrobial susceptibility profiles, serotype distribution and virulence determinants among invasive, non-invasive and colonizing Streptococcus agalactiae (group B streptococcus) from Malaysian patients. Eur J Clin Microbiol Infect Dis 2015; 34(3): 579-84.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
18. Freer J. Preventing perinatal transmission of group B streptococcal disease. JAAPA : official journal of the American Academy of Physician Assistants 2004; 17(3): 47-50; quiz 1-2.	Review, and no bacterial load factor or bacterial molecular marker
19. Friis-Moller A, Busk HE, Korner B, et al. Infections and colonisations with haemolytic streptococci group B in a Danish neonatal intensive care unit. Dan Med Bull 1984; 31(6): 494-9.	No bacterial load factor or bacterial molecular marker
20. Hakansson S, Granlund-Edstedt M, Sellin M, Holm SE. Demonstration and characterization of buoyant-density subpopulations of group B Streptococcus type III. Journal of Infectious Diseases 1990; 161(4): 741-6.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
21. Hakansson S, Holm SE, Wagner M. Density profile of group B streptococci, type III, and its possible relation to enhanced virulence. Journal of Clinical Microbiology 1987; 25(4): 714-8.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
22. Harper IA. The importance of group B streptococci as human pathogens in the British Isles. Journal of clinical pathology 1971; 24(5): 438-41.	Case-report, and no bacterial load factor or bacterial molecular marker
23. Helmig R, Halaburt JT, Uldbjert N, Thomsen AC, Stenderup A. Increased cell adherence of group B streptococci from preterm infants with neonatal sepsis. Obstet Gynecol 1990; 76(5 Pt 1): 825-7.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
24. Hervas JA, Gonzalez L, Gil J, Paoletti LC, Madoff LC, Benedi VJ. Neonatal group B streptococcal infection in Mallorca, Spain. Clinical Infectious Diseases. 1993;16(5):714-8.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
25. Imperi M, Gherardi G, Berardi A, et al. Invasive neonatal GBS infections from an area-based surveillance study in Italy. Clin Microbiol Infect 2011; **17**(12): 1834-9.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
26. Kirmani N, Hafiz S, Jafarey SN, Hassan TJ. Carriage of beta haemolytic streptococci (BHS) in pregnant women and acquisition by neonates. JPMA J Pak Med Assoc 1994; 44(11): 256-7.	No bacterial load factor or bacterial molecular marker
27. Lin FYC, Whiting A, Adderson E, et al. Phylogenetic lineages of invasive and colonizing strains of serotype III group B streptococci from neonates: A multicenter prospective study. Journal of Clinical Microbiology 2006; 44(4): 1257-61.	Unable to distinguish data from those who received IAP and those who did not

Reference	Reason for exclusion
28. Lin F, Sintchenko V, Kong F, Gilbert GL, Coiera E. Commonly used molecular epidemiology markers of Streptococcus agalactiae do not appear to predict virulence. Pathology 2009; 41(6): 576-81.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
29. Manning S, Ki M, Marrs CF, et al. The frequency of genes encoding three putative group B streptococcal virulence factors among invasive and colonizing isolates. Bmc Infectious Diseases 2006; 6.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
30. Marchaim D, Hallak M, Gortzak-Uzan L, Peled N, Riesenberg K, Schlaeffer F. Cell wall proteins of group B Streptococcus and low incidence of neonatal disease in southern Israel. Journal of Reproductive Medicine 2003; 48(9): 697-702.	No bacterial load factor or bacterial molecular marker
31. Meehan M, Cunney R, Cafferkey M. Molecular epidemiology of group B streptococci in Ireland reveals a diverse population with evidence of capsular switching. Eur J Clin Microbiol Infect Dis 2014; 33(7): 1155-62.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
32. Melchers WJG, Bakkers J, Toonen M, van Kuppeveld FJM, Trijbels M, Hoogkamp-Korstanje JAA. Genetic analysis of Streptococcus agalactiae strains isolated from neonates and their mothers. FEMS Immunol Med Microbiol 2003; 36(1-2): 111-3.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
33. Milligan TW, Baker CJ, Straus DC, Mattingly SJ. Association of elevated levels of extracellular neuraminidase with clinical isolates of type III group B streptococci. Infect Immun 1978; 21(3): 738-46.	Unable to distinguish data from early-onset cases to other cases
34. Muller-Vranjes A, Puntaric D, Curzik D, et al. Prevalence and significance of vaginal group B streptococcus colonization in pregnant women from Osijek, Croatia. Coll Antropol 2011; 35(1): 21-6.	No bacterial load factor or bacterial molecular marker
35. Palacios GC, Eskew EK, Solorzano F, Mattingly SJ. Identification of the high-virulence clone of group B streptococci in Mexican isolates by growth characteristics at 40 degrees C. Curr Microbiol 1999; 38(2): 126-31.	Unable to distinguish data from early-onset cases to other cases
36. Palacios GC, Gonzalez MN, Beltran M, Arredondo JL, Torres J, Solorzano F. High-virulence clone of group B streptococci unable to grow at high temperatures is present in serotypes other than type III. Curr Microbiol 2007; 54(1): 42-7.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
37. Palmeiro JK, Dalla-Costa LM, Fracalanzza SE, et al. Phenotypic and genotypic characterization of group B streptococcal isolates in southern Brazil. Journal of Clinical Microbiology 2010; 48(12): 4397-403.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
38. Puopolo KM, Draper D, Wi S, et al. Estimating the Probability of Neonatal Early-Onset Infection on the Basis of Maternal Risk Factors. Pediatrics 2011; 128(5): E1155-E63.	No bacterial load factor or bacterial molecular marker
39. Regan JA, Klebanoff MA, Nugent RP, et al. Colonization with group B streptococci in pregnancy and adverse outcome. VIP Study Group. Am J Obstet Gynecol 1996; 174(4): 1354-60.	Unable to distinguish data from those who received IAP and those who did not
40. Siauw C, Kobsar A, Dornieden C, et al. Group B streptococcus isolates from septic patients and healthy carriers differentially activate platelet signaling cascades. Thromb Haemost 2006; 95(5): 836-49.	Unable to distinguish data from early-onset cases to other cases
41. Smith TC, Roehl SA, Pillai P, Li S, Marrs CF, Foxman B. Distribution of novel and previously investigated virulence genes in colonizing and invasive isolates of Streptococcus agalactiae. Epidemiology and Infection 2007; 135(6): 1046-54.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)

Reference	Reason for exclusion
42. Teixeira LA, Figueiredo AM, Ferreira BT, et al. Sialic acid content and surface hydrophobicity of group B streptococci. Epidemiol Infect 1993; 110(1): 87-94.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
43. Towers CV, Garite TJ, Friedman WW, Pircon RA, Nageotte MP. Comparison of a rapid enzyme-linked immunosorbent assay test and the Gram stain for detection of group B streptococcus in high-risk antepartum patients. Am J Obstet Gynecol 1990; 163(3): 965-7.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
44. Valentin-Weigand P, Chhatwal GS. Correlation of epithelial cell invasiveness of group B streptococci with clinical source of isolation. Microb Pathog 1995; 19(2): 83-91.	Unable to distinguish data from early-onset cases to other cases
45. van der Mee-Marquet N, Domelier AS, Mereghetti L, et al. Prophagic DNA fragments in Streptococcus agalactiae strains and association with neonatal meningitis. Journal of Clinical Microbiology 2006; 44(3): 1049-58.	Bacterial load or bacterial molecular marker not related to transmission (from mother to baby) or transition (from early-onset colonisation to early onset GBS disease)
46. van Elzakker E, Yahiaoui R, Visser C, et al. Epidemiology of and prenatal molecular distinction between invasive and colonizing group B streptococci in The Netherlands and Taiwan. Eur J Clin Microbiol Infect Dis 2009; 28(8): 921-8.	Unable to distinguish data from early-onset cases to other cases
47. Weindling AM, Hawkins JM, Coombes MA, Stringer J. Colonisation of babies and their families by group B streptococci. Br Med J (Clin Res Ed) 1981; 283(6305): 1503-5.	No bacterial load factor or bacterial molecular marker

GBS: group B *Streptococcus*; IAP: Intrapartum antibiotic prophylaxis

Appendix 11. List of studies excluded from the systematic review for question 20 (n=227), with reason

	Reference	Reason for exclusion
1.	Aard LA, Saed F. Low-incidence cesarean section: 12-year experience. Mayo Clin Proc 1975; **50**(7): 365-9.	Prophylaxis for Caesarean section
2.	Adeniran AS, Aboyeji AP, Fawole AA, Adesiyun OO, Saidu R. Role of Risk-Based Approach in the Prevention of Vertical Transmission of Neonatal Sepsis. Niger Postgrad Med J 2015; **22**(2): 88-92.	>10% had symptoms in labour (intrapartum fever)
3.	Andrews WW, Hauth JC, Cliver SP, Savage K, Goldenberg RL. Randomized clinical trial of extended spectrum antibiotic prophylaxis with coverage for Ureaplasma urealyticum to reduce post-cesarean delivery endometritis. Obstet Gynecol 2003; **101**(6): 1183-9.	Prophylaxis for Caesarean section
4.	Anonymous. Prophylactic antibiotics in caesarean section. Br Med J 1973; **2**(5868): 675-6.	Consensus statement
5.	Anonymous. Obesity in pregnancy. Obstet Gynecol 2015; **126**(6): e112-e26.	Review
6.	Anteby SO, Birkenfeld A, Weinstein D. Post cesarean section urinary tract infections, risk factors and prophylactic antibiotic treatment. Clin Exp Obstet Gynecol 1984; **11**(4): 161-4.	Prophylaxis for Caesarean section
7.	Apgar BS, Greenberg G, Yen G. Prevention of group B streptococcal disease in the newborn. Am Fam Physician 2005; **71**(5): 903-10.	Review
8.	Apuzzio JJ, Ganesh VV, Pelosi MA, Frisoli G. The effect of prophylactic antibiotics on risk factors for endomyometritis in adolescent patients undergoing cesarean section. Journal of adolescent health care : official publication of the Society for Adolescent Medicine, 1984.	Prophylaxis for Caesarean section
9.	Ayangade O. Antibiotic prophylaxis in high-risk obstetrics. J Natl Med Assoc 1977; **69**(11): 793-5.	Unable to identify timing of antibiotics
10.	Ayangade O. Long vs short-course antibiotic prophylaxis in cesarean section: a comparative clinical study. J Natl Med Assoc 1979; **71**(1): 71-3.	Prophylaxis for Caesarean section
11.	Battarino O, Battarino A. [Short-term antibiotic prophylaxis in cesarean section]. Minerva ginecologica, 1988.	Full text not in English
12.	Beattie PG, Rings TR, Hunter MF, Lake Y. Risk factors for wound infection following caesarean section. Aust N Z J Obstet Gynaecol 1994; **34**(4): 398-402.	Prophylaxis for Caesarean section
13.	Benigno BB, Ford LC, Lawrence WD, Ledger WJ, Ling FW, McNeeley SG. A double-blind, controlled comparison of piperacillin and cefoxitin in the prevention of postoperative infection in patients undergoing cesarean section. Surg Gynecol Obstet, 1986.	Prophylaxis for Caesarean section
14.	Benjamin DK, Stoll BJ, Gantz MG, et al. Neonatal Candidiasis: Epidemiology, Risk Factors, and Clinical Judgment. Pediatrics 2010; **126**(4): E865-E73.	Unable to distinguish intrapartum antibiotics with other timings
15.	Berardi A, Rossi C, Creti R, et al. Group B Streptococcal colonization in 160 mother-baby pairs: A prospective cohort study. J Pediatr 2013; **163**(4): 1099-104.e1.	No data on adverse events
16.	Berkeley AS, Hirsch JC, Freedman KS, Ledger WJ. Cefotaxime for cesarean section prophylaxis in labor. Intravenous administration vs. lavage. Journal of Reproductive Medicine for the Obstetrician and Gynecologist 1990; **35**(3): 214-8.	Prophylaxis for Caesarean section
17.	Bibi M, Megdiche H, Ghanem H, et al. [Antibiotic prophylaxis in a priori cesarean sections without a high risk of infection. Experiences of a Tunisian maternity department]. Journal de gynécologie, obstétrique et biologie de la reproduction, 1994.	Full text not in English
18.	Birkenfeld A, Anteby SO. The effect of ampicillin and colistin on post-Caesarean section endometritis with identification of possible risk factors. Aust N Z J Obstet Gynaecol 1983; **23**(4): 204-7.	Prophylaxis for Caesarean section
19.	Block BS, Mercer LJ, Ismail MA, Moawad AH. Clostridium difficile-associated diarrhea follows perioperative prophylaxis with cefoxitin. Am J Obstet Gynecol 1985; **153**(8): 835-8.	>10% prophylaxis for Caesarean section

Reference	Reason for exclusion
20. Boothby R, Benrubi G, Ferrell E. Comparison of intravenous cefoxitin prophylaxis with intraoperative cefoxitin irrigation for the prevention of post-cesarean-section endometritis. Journal of Reproductive Medicine for the Obstetrician and Gynecologist 1984; **29**(11): 830-2.	Prophylaxis for Caesarean section
21. Bourgeois FJ, Pinkerton JA, Andersen W, Thiagarajah S. Antibiotic irrigation prophylaxis in the high-risk cesarean section patient. Am J Obstet Gynecol 1985; 153(2): 197-201.	Prophylaxis for Caesarean section
22. Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. N Engl J Med 1986; 314(26): 1665-9.	>10% participants had symptoms in labour (maternal fever)
23. Bromiker R, Ernest N, Meir MB, et al. Correlation of bacterial type and antibiotic sensitivity with maternal antibiotic exposure in early-onset neonatal sepsis. Neonatology 2013; **103**(1): 48-53.	>10% participants had symptoms in labour (maternal fever)
24. Brown J, Thompson M, Sinnya S, et al. Pre-incision antibiotic prophylaxis reduces the incidence of post-caesarean surgical site infection. J Hosp Infect 2013; **83**(1): 68-70.	Prophylaxis for Caesarean section
25. Brozanski BS, Jones JG, Krohn MA, Sweet RL. Effect of a screening-based prevention policy on prevalence of early-onset group B streptococcal sepsis. Obstet Gynecol 2000; **95**(4): 496-501.	No data on adverse events
26. Buchholz NP, Daly-Grandeau E, Huber-Buchholz MM. Urological complications associated with caesarean section. Eur J Obstet Gynecol Reprod Biol 1994; **56**(3): 161-3.	Prophylaxis for Caesarean section
27. Busowski JD, Porter KB, Pendergraft S, O'Brien WF, Vodra J. Antibiotic prophylaxis for Cesarean delivery: a randomized trial of cefotetan, ampicillin-sulbactam and ciprofloxacin. Prenat Neonatal Med 2000; **5**(6): 357-62.	Prophylaxis for Caesarean section
28. Carlson C, Duff P. Antibiotic prophylaxis for cesarean delivery: is an extended-spectrum agent necessary? Obstet Gynecol 1990; **76**(3 Pt 1): 343-6.	Prophylaxis for Caesarean section
29. Carney E. Antibiotic prophylaxis in obstetrics and gynecology. J Med Assoc State Ala 1975; 44(9): 493-4, 9.	Review
30. Cassidy-Bushrow AE, Sitarik A, Levin AM, et al. Maternal group B Streptococcus and the infant gut microbiota. J Dev Orig Health Dis 2016; 7(1): 45-53.	>10% neonates received antibiotics after birth
31. Chan AC, Leung AK, Chin RK, Chang AM. Single dose prophylactic antibiotics in caesarean sections. Aust N Z J Obstet Gynaecol 1989; **29**(2): 107-9.	Prophylaxis for Caesarean section
32. Chang PL, Newton ER. Predictors of antibiotic prophylactic failure in post-cesarean endometritis. Obstet Gynecol 1992; **80**(1): 117-22.	Prophylaxis for Caesarean section
33. Chantharojwong P. An efficacy study of ampicillin versus cefazolin prophylaxis in patients undergoing cesarean section. J Med Assoc Thai 1993; **76**(3): 165-70.	Prophylaxis for Caesarean section
34. Chimura T. The efficacy of ceftriaxone administered for prophylaxis of postoperative infection and infectious diseases in obstetrics and gynecology. J Chemother 1989; **1**(4 Suppl): 1039-41.	Antibiotics administered after birth
35. Chittacharoen A, Manonai J, Suthutvoravut S, Phaupradit W. Single-dose amoxycillin-clavulanic acid vs. ampicillin prophylaxis in emergency cesarean section. International Journal of Gynecology and Obstetrics 1998; **62**(3): 249-54.	Prophylaxis for Caesarean section
36. Conover WB, Moore TR. Comparison of irrigation and intravenous antibiotic prophylaxis at cesarean section. Obstet Gynecol 1984; **63**(6): 787-91.	Prophylaxis for Caesarean section
37. Conturso R, Valsecchi A, De Lalla F. Evaluation of mezlocillin versus placebo as a prophylactic agent in cesarean section. Chemioterapia 1987; **6**(2 Suppl): 611-3.	Prophylaxis for Caesarean section
38. Currier JS, Tosteson TD, Platt R. Cefazolin compared with cefoxitin for cesarean section prophylaxis: the use of a two-stage study design. J Clin Epidemiol 1993; **46**(7): 625-30.	Prophylaxis for Caesarean section
39. Cyrkowicz A, Rytwińska E, Nytko J, Słowińska-Zabówka M. [Preparation for delivery in patients with missed labor considering low-dose heparin and prostaglandins]. Przegląd lekarski, 1996.	Full text not in English
40. D'Angelo LJ, Sokol RJ. Short- versus long-course prophylactic antibiotic treatment in Cesarean section patients. Obstet Gynecol 1980; **55**(5): 583-6.	Prophylaxis for Caesarean section

Reference	Reason for exclusion
41. Daley AJ, Isaacs D. Ten-year study on the effect of intrapartum antibiotic prophylaxis on early onset group B streptococcal and Escherichia coli neonatal sepsis in Australasia. Pediatr Infect Dis J 2004; **23**(7): 630-4.	Population level ecological study
42. Dashefsky B. Prophylaxis against neonatal group B streptococcal disease. Pediatr Infect Dis J 1990; **9**(2): 147-9.	Letter
43. Davey P. Antimicrobial prophylaxis for caesarean section - the unanswered questions. Journal of Obstetrics and Gynaecology 1992; **12**(SUPPL. 1): S21-S3.	Review
44. De Luca C, Buono N, Santillo V, et al. Screening and management of maternal colonization with Streptococcus agalactiae: an Italian cohort study. J Matern-Fetal Neonatal Med 2016; **29**(6): 911-5.	No data on adverse events
45. Decavalas G, Maroulis G, Papaioannou C, Papapetropoulou M. Comparative study of ceftriaxone versus cefamandole for pre-operative prophylaxis of infections in patients undergoing cesarean section or vaginal hysterectomy. J Chemother 1989; **1**(4 Suppl): 1048-50.	Prophylaxis for Caesarean section
46. Dlamini LD, Sekikubo M, Tumukunde J, et al. Antibiotic prophylaxis for caesarean section at a Ugandan hospital: a randomised clinical trial evaluating the effect of administration time on the incidence of postoperative infections. BMC Pregnancy & Childbirth 2015; **15**: 91.	Prophylaxis for Caesarean section
47. Donnenfeld AE, Otis C, Weiner S. Antibiotic prophylaxis in cesarean section. Comparison of intrauterine lavage and intravenous administration. The Journal of reproductive medicine, 1986.	Prophylaxis for Caesarean section
48. Duff P, Park RC. Antibiotic prophylaxis for cesarean section in a military population. Mil Med 1980; **145**(6): 377-81.	Prophylaxis for Caesarean section
49. Dumas AM, Girard R, Ayzac L, et al. Effect of intrapartum antibiotic prophylaxis against group B streptococcal infection on comparisons of rates of endometritis and urinary tract infection in multicenter surveillance. Infect Control Hosp Epidemiol 2008; **29**(4): 327-32.	No data on adverse events
50. Easmon CSF, Hastings MJG, Deeley J. The effect of intrapartum chemoprophylaxis o vertical transmission of group B streptococci. Br J Obstet Gynaecol 1983; **90**(7): 633	No data on adverse events
51. Ecker KL, Donohue PK, Kim KS, Shepard JA, Aucott SW. The impact of group B streptococcus prophylaxis on late-onset neonatal infections. J Perinatol 2013; 33(3): 206-11.	>10% participants had symptoms in labour (prolonged rupture of membranes)
52. Edwards RK, Clark P, Sistrom CL, Duff P. Intrapartum antibiotic prophylaxis 1: Relative effects of recommended antibiotics on gram-negative pathogens. Obstet Gynecol 2002; 100(3): 534-9.	>10% antibiotics received antibiotics before labour
53. Elliott JP, Flaherty JF. Comparison of lavage or intravenous antibiotics at cesarean section. Obstet Gynecol, 1986.	Prophylaxis for Caesarean section
54. Elliott JP, Freeman RK, Dorchester W. Short versus long course of prophylactic antibiotics. Am J Obstet Gynecol 1982; **143**(7): 740-4.	>10% prophylaxis for Caesarean section
55. Elyan A, Mahran M, el-Maraghy M, Abou-Seeda M. Prophylactic intravenous metronidazole in cesarean section. Chemioterapia 1984; 3(1): 67-70.	Prophylaxis for Caesarean section
56. Engel K, Karschnia R. Bacterial flora changes resulting from antimicrobial treatment. Journal of Obstetrics and Gynaecology 1986; **6**(SUPPL. 1): S6-S8.	>10% prophylaxis for Caesarean section
57. Engel K, Karschnia R, Rauch U, Amir B. Efficacy of a high dosage short course prophylactic treatment for postoperative infection complications in cesarean section - using a combination of mezlocillin and oxacillin (Optocillin). Chemioterapia 1982; 1(4 Suppl.): No. 326.	Prophylaxis for Caesarean section
58. Escobedo Lobatón JM, Rodríguez Hinojosa DE, Kistner Garza AM, Benavides de Anda L. [Prophylactic use of antibiotics in cesarean section]. Ginecología y obstetricia de México, 1991.	Full text not in English
59. Faro S, Cox SM, Phillips L, Baker J. Influence of antibiotic prophylaxis on vaginal microflora. Journal of Obstetrics and Gynaecology 1986; 6(SUPPL. 1): S4-S6.	>10% received antibiotics for Caesarean section
60. Faro S, Martens MG, Hammill HA, Riddle G, Tortolero G. Antibiotic prophylaxis: is there a difference? Am J Obstet Gynecol 1990; **162**(4): 900-7; discussion 7-9.	>10% prophylaxis for Caesarean section

Reference	Reason for exclusion
61. Farret TCF, Dalle J, da Silva Monteiro V, Riche CVW, Antonello VS. Risk factors for surgical site infection following cesarean section in a Brazilian Women's Hospital: A case-control study. Braz J Infect Dis 2015; **19**(2): 113-7.	Prophylaxis for Caesarean section
62. Fedele L, Acaia B, Marchini M, Baglioni A, Frigoli A, De Pascale A. Cefotetan and ceftriaxone for single-dose prophylaxis in cesarean section. J Chemother 1989; **1**(4 Suppl): 1042-3.	Prophylaxis for Caesarean section
63. Fejgin MD, Markov S, Goshen S, Segal J, Arbel Y, Lang R. Antibiotic for cesarean section: the case for 'true' prophylaxis. Int J Gynaecol Obstet 1993; **43**(3): 257-61.	Prophylaxis for Caesarean section
64. Felton DJ, Williams JD. Prophylactic ampicillin the the surgical induction of labour. J Obstet Gynaecol Br Commonw 1967; **74**(6): 862-7.	Antibiotics administered before labour
65. Fonseca SNS, Sofia MH, Quintana S, Nogueira FDS, Levin AS. Successful control program to implement the appropriate antibiotic prophylaxis for cesarean section. Rev Inst Med Trop Sao Paulo 2008; **50**(2): 79-82.	Prophylaxis for Caesarean section
66. Ford LC. Cost of antibiotic prophylaxis in cesarean section. Drug Intell Clin Pharm 1986; **20**(7-8): 592-3.	Prophylaxis for Caesarean section
67. Ford LC, Tabsh K, Lebherz TB. Use of antibiotics for prophylaxis with caesarean section. Journal of Obstetrics and Gynaecology 1986; 6(SUPPL. 1): S68-S70.	Prophylaxis for Caesarean section
68. Francis C, Mumford M, Strand ML, Moore ES, Strand EA. Timing of prophylactic antibiotic at cesarean section: a double-blinded, randomized trial. J Perinatol 2013; 33(10): 759-62.	Prophylaxis for Caesarean section
69. Freeman GM. The efficacy of prophylactic antibiotics in high-risk patients undergoing cesarean section. J-Am-Osteopath-Assoc, 1982.	Prophylaxis for Caesarean section
70. Galask RP, Weiner C, Petzold CR. Comparison of single-dose cefmetazole and cefotetan prophylaxis in women undergoing primary caesarean section. J Antimicrob Chemother 1989; **23 Suppl D**: 105-8.	Prophylaxis for Caesarean section
71. Gall SA. The efficacy of prophylactic antibiotics in cesarean section. Am J Obstet Gynecol, 1979.	Prophylaxis for Caesarean section
72. Gall SA, Hill GB. Single-dose versus multiple-dose piperacillin prophylaxis in primary cesarean operation. Am J Obstet Gynecol 1987; **157**(2): 502-6.	S Prophylaxis for Caesarean section
73. Gerard P, Verghote-D'Hulst M, Bachy A, Duhaut G. Group B streptococcal colonization of pregnant women and their neonates. Epidemiological study and controlled trial of prophylactic treatment of the newborn. Acta Paediatr Scand, 1979.	Antibiotics administered after birth
74. Gerber B, Retzke F, Wilken H. [Effectiveness of perioperative preventive use of antibiotics with ampicillin/gentamycin or cefotiam in abdominal cesarean section]. Zentralblatt für Gynäkologie, 1989.	Full text not in English
75. Gerstner G, Kofler E, Huber J. [Perioperative metronidazole-prophylaxis for cesarian section (author's transl]. Zeitschrift für Geburtshilfe und Perinatologie, 1980.	Full text not in English
76. Ghuman M, Rohlandt D, Joshy G, Lawrenson R. Post-caesarean section surgical site infection: Rate and risk factors. N Z Med J 2011; **124**(1339): 32-6.	Prophylaxis for Caesarean section
77. Gibbs RS, DeCherney AH, Schwarz RH. Prophylactic antibiotics in cesarean section: a double-blind study. Am J Obstet Gynecol 1972; **114**(8): 1048-53.	Prophylaxis for Caesarean section
78. Gibbs RS, Hunt JE, Schwarz RH. A follow-up study on prophylactic antibiotics in cesarean section. Am J Obstet Gynecol 1973; **117**(3): 419-22.	Prophylaxis for Caesarean section
79. Gibbs RS, Weinstein AJ. Bacteriologic effects of prophylactic antibiotics in cesarean section. Am J Obstet Gynecol, 1976.	Prophylaxis for Caesarean section
80. Gidiri MF, Ziruma A. A randomized clinical trial evaluating prophylactic single-dose vs prolonged course of antibiotics for caesarean section in a high HIV-prevalence setting. J Obstet Gynaecol 2014; **34**(2): 160-4.	Prophylaxis for Caesarean section
81. Giuliani B, Periti E, Mecacci F. Antimicrobial prophylaxis in obstetric and gynecological surgery. J Chemother 1999; **11**(6): 577-80.	Surgical prophylaxis
82. Glasgow TS, Speakman M, Firth S, James B, Byington CL, Young PC. Clinical and economic outcomes for term infants associated with increasing administration of antibiotics to their mothers. Paediatr Perinat Epidemiol 2007; **21**(4): 338-46.	Unclear when antibiotic was given

Reference	Reason for exclusion
83. Gonen R, Samberg I, Levinski R. Effect of irrigation or intravenous antibiotic prophylaxis on infectious morbidity at cesarean section. Obstet Gynecol 1986; **67**(4): 545-8.	Prophylaxis for Caesarean section
84. Gong SP, Guo HX, Zhou HZ, Chen L, Yu YH. Morbidity and risk factors for surgical site infection following cesarean section in Guangdong Province, China. J Obstet Gynaecol Res 2012; **38**(3): 509-15.	Prophylaxis for Caesarean section
85. Gonik B, Shannon RL, Shawar R, Costner M, Seibel M. Why patients fail antibiotic prophylaxis at cesarean delivery: histologic evidence for incipient infection. Obstet Gynecol 1992; **79**(2): 179-84.	Prophylaxis for Caesarean section
86. Gordon HR, Phelps D, Blanchard K. Prophylactic cesarean section antibiotics: maternal and neonatal morbidity before or after cord clamping. Obstet Gynecol 1979; **53**(2): 151-6.	Prophylaxis for Caesarean section
87. Gordon SF, Russell J. A randomized controlled study comparing ceftizoxime, cefamandole, and cefoxitin in obstetric and gynecological surgery: A preliminary report. J Antimicrob Chemother 1982; **10**(Suppl. C): 289-92.	Surgical prophylaxis
88. Green SL, Sarubbi FA, Jr., Bishop EH. Prophylactic antibiotics in high-risk cesarean section. Obstet Gynecol 1978; **51**(5): 569-72.	Prophylaxis for Caesarean section
89. Gronlund MM, Lehtonen OP, Eerola E, Kero P. Fecal microflora in healthy infants born by different methods of delivery: Permanent changes in intestinal flora after cesarean delivery. J Pediatr Gastroenterol Nutr 1999; **28**(1): 19-25.	>10% participants had elective caesarean section
90. Grossman Donowitz L, Norris SM. The efficacy of antibiotic prophylaxis in the prevention of post-cesarean section endometritis. *Infect Control* 1985; **6**(5): 189-93.	Prophylaxis for Caesarean section
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Reference	Reason for exclusion
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Reference	Reason for exclusion
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176. Saezllorens X, Ahchu MS, Castano E, et al. Intrapartum Prophylaxis with Ceftriaxone Decreases Rates of Bacterial-Colonization and Early-Onset Infection in Newborns. Clin Infect Dis 1995; **21**(4): 876-80.	>10% symptomatic (prolonged rupture of membranes)
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178. Schrag SJ, Cutland CL, Zell ER, et al. Risk factors for neonatal sepsis and perinatal death among infants enrolled in the prevention of perinatal sepsis trial, Soweto, South Africa. Pediatr Infect Dis J 2012; **31**(8): 821-6.	>10% symptomatic (prolonged rupture of membrane, foul smelling vaginal discharge)
179. Schrag SJ, Hadler JL, Arnold KE, Martell-Cleary P, Reingold A, Schuchat A. Risk factors for invasive, early-onset Escherichia coli infections in the era of widespread intrapartum antibiotic use. Pediatrics 2006; **118**(2): 570-6.	>10% symptomatic (intrapartum fever, prolonged rupture of membrane)
180. Schuchat A, Zywicki SS, Dinsmoor MJ, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: A multicenter case-control study. Pediatrics 2000; **105**(1): 21-6.	>10% symptomatic (intrapartum fever, prolonged rupture of membrane)

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186. Smith AM, Cox CWFM. Necrotising fasciitis following caesarean section. Journal of Obstetrics and Gynaecology 1992; **12**(4): 246-7.	Case report
187. Spandorfer SD, Graham E, Forouzan I. Postcesarean endometritis. Clinical risk factors predictive of positive blood cultures. J Reprod Med 1996; **41**(11): 797-800.	Prophylaxis for Caesarean section
188. Spreafico P, Scian A, Epis A, Vassen L, Bonazzi C, Lovotti M. Cesarean section: antibiotic prophylaxis with ceftezole. Chemioterapia 1987; **6**(2 Suppl): 613-6.	Prophylaxis for Caesarean section
189. Stage AH, Glover DD, Vaughan JE. Low-dose cephradine prophylaxis in obstetric and gynecologic surgery. J Reprod Med 1982; **27**(3): 113-9.	Surgical prophylaxis
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191. Stiver HG, Forward KR, Livingstone RA. Double blind placebo-controlled multicentre comparison of cefoxitin vs cefazolin prophylaxis against post-cesarean section infection. Clinical and Investigative Medicine 1982; **5**(2-3): 34B.	Abstract
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195. Suonio S, Saarikoski S, Vohlonen I, Kauhanen O. Risk factors for fever, endometritis and wound infection after abdominal delivery. Int J Gynaecol Obstet 1989; **29**(2): 135-42.	Prophylaxis for Caesarean section
196. Szalontay AS. [Antibiotic prophylaxis in cesarean section]. Revista medico-chirurgicală a Societăţii de Medici şi Naturalişti din Iaşi, 1997.	Full text not in English
197. Tassi PG, Tarantini M, Rampinelli F, et al. Piperacillin in antibiotic prophylaxis: a single-dose administration for cesarean section. J Chemother 1989; 1(4 Suppl): 1025-6.	Prophylaxis for Caesarean section
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199. Teo SM, Mok D, Pham K, et al. The Infant Nasopharyngeal Microbiome Impacts Severity of Lower Respiratory Infection and Risk of Asthma Development. Cell Host Microbe 2015; **17**(5): 704-15.	Unclear when antibiotics were given and delivery mode

Reference	Reason for exclusion
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202. To WW, Lau WN. A protocol of selective antibiotic prophylaxis for caesarean section based on risk factors. Aust N Z J Obstet Gynaecol 2001; **41**(4): 402-6.	Prophylaxis for Caesarean section
203. Towers CV, Cart MH, Padilla G, Asrat T. Potential consequences of widespread antepartal use of ampicillin. Am J Obstet Gynecol 1998; **179**(4): 879-83.	Unable to distinguish mothers treated in labour from mother treated in pregnancy as well
204. Tsai CH, Chen YY, Wang KG, Chen CY, Chen CP. Characteristics of early-onset neonatal sepsis caused by Escherichia coli. Taiwan J Obstet Gynecol 2012; **51**(1): 26-30.	Unable to distinguish women who had emergency caesarean section from those that had elective caesarean section
205. Tully JL, Klapholz H, Baldini LM, Friedland GH. Perioperative use of cefoxitin in primary cesarean section. J Reprod Med 1983; **28**(12): 827-32.	Prophylaxis for Caesarean section
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207. Turner MJ. Prophylactic antibiotics for caesarean section and hysterectomy. Journal of Obstetrics and Gynaecology 1994; **14**(1): 54-5.	Editorial
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227. Zhang J, Johnson CD, Hoffman M. Cervical cerclage in delayed interval delivery in a multifetal pregnancy: a review of seven case series. Eur J Obstet Gynecol Reprod Biol 2003; **108**(2): 126-30.	Review of case series about cervical cerclage for multiple births

GBS: group B *Streptococcus*; IAP: Intrapartum antibiotic prophylaxis.

Appendix 12. Characteristics of 25 included observational studies in rapid review

Bauserman 2013[114]	
Methods	Retrospective multicenter cohort study. Data source: Chart review of all blood, urine, and cerebrospinal fluid culture results from infants before and after universal IAP recommendations; clinical progress notes. Setting: 322 neonatal intensive care units managed by the Pediatrix Medical Group in the United States. Study period: 1997-2010 (Before universal IAP recommendations: 1997-2001; after universal IAP recommendations: 2002-2010).
Population	Inclusion criteria: Infants admitted from 1997-2010 to 322 neonatal intensive care units managed by the Pediatrix Medical Group. Exclusion criteria: none. Inclusion / Exclusion (study): 716,407 admissions / none excluded. Inclusion / Exclusion (analysis): 716,407 admissions / none excluded. Inclusion / Exclusion (review questions): 21) 716,407 admissions / none excluded.
Exposure	21) 1997-2001: Risk-based screening for GBS & IAP. 2002-2010: Universal GBS screening & IAP.
Outcomes	21) Clinical effectiveness of GBS screening on EOGBS-related mortality and morbidity, neonatal sepsis and neonatal sepsis-related mortality. Early-onset serious bacterial infections: Positive blood, urine (obtained from a catheterization or suprapubic tap), or CSF culture for GBS or *E. coli* within the first 3 postnatal days. Exclusion of urine cultures obtained from bag specimens. Cultures that were positive for the same organism within a 21-day period were considered as a single episode of infection.

Berardi 2013[40]	
Methods	Prospective cohort study. Setting: 1 nursery of a tertiary care centre, Italy. Study period: Enrollment began 20 July 2008; follow-up completed on 1 June 2010. Follow-up: 8 weeks postpartum.
Population	Inclusion criteria: Singleton pregnancy; antenatal screening at 35-37 weeks gestation (or GBS bacteriuria during pregnancy or a previous infant with GBS disease); a residential address within 15 km of the hospital; and sufficient communication skills in the national language. Exclusion criteria NR. Inclusion / Exclusion (study): 182 mother-baby pairs; GBS non-carriers were enrolled according to a 1:2 ratio compared with GBS carriers / 6,682 excluded: reason NR. Inclusion / Exclusion (analysis): 160 mother-baby pairs / 22 excluded: 12 lost to follow-up, 10 missing data. Inclusion / Exclusion (review questions): 14) 16 colonised neonates during hospitalisation without IAP / 144 excluded: 3 colonised neonates with IAP; 141 not colonised during hospitalisation. 17b) 76 women with antenatal screening and no IAP / 84 excluded: 10 no antenatal screening; 74 IAP. 18) 94 women with positive antenatal screening / 66 excluded: 10 no antenatal screening; 56 negative antenatal screening.
Index test / Reference standard (17b)	Index test: 35-37 weeks; low vaginal and rectal swabs; selective enrichment with Todd-Hewitt broth. Reference standard: EOGBS presence: NR (Blood cultures were analysed with an automated system. “Case 2 … presented with early-onset clinical sepsis 20 hours after birth…”). EOGBS absence: NR. All neonates were followed-up until 8 weeks postpartum.
Exposure	18) Standard dose of ampicillin (2 g intravenously plus 1 g intravenously every 4 hours until delivery) (n=70). No IAP (n=24).
Outcomes	14) Colonised babies affected by EOGBS. Neonatal GBS colonisation: - Swabs from throat, ear and rectum; 10-24 hours of birth; rectal swabs: selective enrichment Todd-Hewitt broth; throat and ear swabs: nonselective chromogenic culture media (chromID StreptoB). - Swabs from throat and rectum, 48-72 hours after birth/nursery discharge; rectal swabs: selective enrichment Todd-Hewitt broth; throat and ear swabs: nonselective chromogenic culture media (chromID StreptoB). 17b) Predictive value of selective antenatal culture screening for EOGBS. 18) Effectiveness of IAP in preventing EOGBS related morbidity and mortality in screen-detected populations.

British Paediatric Surveillance Unit (BPSU) 2016[39]	
Methods	Prospective, enhanced, active surveillance undertaken through the British Paediatric Surveillance Unit (BPSU), microbiology reference laboratories, and microbiology laboratory notifications to the public health agencies of England, Wales, Scotland, Northern Ireland (NI), and the Republic of Ireland (RoI). Data source: Monthly "orange card" system sent to all consultant paediatricians in the British Isles; interrogation of national surveillance database routinely used by hospital laboratories in England and Wales to voluntarily report infections electronically to PHE; case ascertainment from public health agencies of Scotland, NI, and RoI (in both NI and RoI, invasive GBS disease is a notifiable condition); reference laboratories which receive GBS isolates for confirmation and serotyping; contact of all individual laboratories at the end of the surveillance to confirm completeness. Setting: England, Wales, Scotland, Northern Ireland and Republic of Ireland. Study period: April 2014 to April 2015 inclusive (13 months).
Population	Inclusion criteria: All cases of invasive GBS infections in infants younger than 90 days in the UK and the Republic of Ireland between April 2014 and April 2015 inclusive. Exclusion criteria NR. Inclusion / Exclusion (study): 856 / NR Inclusion / Exclusion (analysis): see below Inclusion / Exclusion (review questions): 1) 518 EOGBS cases; serotypes: 229 EOGBS cases (44.2%) with serotype information. / 338 LOGBS cases excluded; 289 EOGBS cases (55.8%) without serotype information. 2) 429 EOGBS cases (82.8%) with available risk factor information. / 338 LOGBS cases excluded; 89 EOGBS cases (17.2%) without available risk factor information. 3, 4, 6) 518 EOGBS cases. / 338 LOGBS cases excluded. 5) 429? (415?) EOGBS cases (82.8%? 80.1%?) with available risk factor information. / 338 LOGBS cases excluded; 89? (103?) EOGBS cases (17.2%? 19.9%?) without available risk factor information.
Outcomes	1) EOGBS incidence; serotype distribution and sequence types of GBS isolates. 2) EOGBS distribution by maternal risk factors. 3) Clinical presentation of EOGBS. 4) EOGBS case fatality rate. 5) Mortality attributable to EOGBS distributed by maternal risk factors. 6) Short-term morbidities associated with EOGBS. 8) Association between EOGBS clinical presentation and morbidity outcomes. Nominator: Isolation of GBS from a normally sterile site in infants <7 days of age. For infants having more than one episode of GBS infection, only the first episode was used for calculation of incidence and risk-factor data. Denominator: Live births in 2014 (after adjustment for the 13-month surveillance period) obtained from ONS, National Records of Scotland, Republic of Ireland Central Statistics Office, and Northern Ireland Statistics and Research Agency.

De Luca 2016[80]	
Methods	Prospective cohort study. Data source: Medical records. Setting: Obstetrics and Gynecology Unit and the Neonatology Intensive Care Unit of Cardarelli Hospital, Campobasso, Italy. Study period: July 2013 to December 2013.
Population	Inclusion criteria: Pregnant women admitted to Obstetrics and Gynecology Unit of Cardarelli Hospital for delivery between July and December 2013. Exclusion criteria: NR; For analysis: stillbirth; missing data. Inclusion / Exclusion (study): 535 women / none excluded. Inclusion / Exclusion (analysis): 468 (87%) women and 475 live births / 67 excluded: 2 stillbirths; 65 missing data on study outcomes. Inclusion / Exclusion (review questions): 18) 85 positive at GBS screening and planned vaginal birth / 383 excluded: 11 caesarean deliveries before onset of labour with intact amniotic membranes; 150 no antenatal GBS screening; 222 negative antenatal GBS culture.
Exposure	18) Ampicillin as first-line drug, with a dosage of 2 g intravenously followed by 1 g intravenously every 4 h until delivery. Penicillin-allergic mothers treated with clindamycin or vancomycin intravenously. Adequate IAP: ≥4 h before delivery (n=47) Incomplete IAP: <4 hours before delivery (n=19). No IAP (n=19).
Outcomes	18) Effectiveness of IAP in preventing EOGBS related morbidity and mortality in screen-detected populations. EOGBS: GBS infection early-onset disease occurring during the first week of life. Diagnostic assessment included blood cultures, complete blood counts, chest X-rays, and lumbar punctures.

Eastwood 2014[46]	
Methods	Retrospective cohort study, audit. Setting: Northern Ireland maternity units. Data source: Northern Ireland Health Information Systems. Neonatal work stream (review questions 1-5, 7): Review of maternal and infant case notes; positive cultures identified by laboratories throughout all HSC Trusts. Cross check performed using the Neonatal Intensive Care Outcomes Research and Evaluation database (NICORE), Public Health Agency (PHA) provided a list of cases voluntarily reported to them by each Trust during the audit time-frame. Pathology work stream (review question 9, 10): Antenatal and intrapartum stillbirths referred for autopsy to the Regional Paediatric Pathology Service between 2009 and 2010 inclusive. Study period: Neonatal work stream: 2008 and 2010 inclusive (3 years); Pathology work stream: 2009 and 2010 inclusive (2 years).
Population	Inclusion criteria: Neonatal work stream: Culture-positive cases (blood or CSF) of GBS in babies aged 0-89 days between 2008 and 2010 inclusive. Pathology work stream: Antenatal and intrapartum stillbirths referred for autopsy to the Regional Paediatric Pathology Service between 2009 and 2010 inclusive: stillbirths related to any infection i) histopathological evidence of inflammation in the placenta or fetal tissues; ii) a positive culture of any organism from the baby (usually heart, lung or gastric swabs). Review of cases with i) or ii) by an independent Consultant Obstetrician and a Consultant Paediatric Pathologist; assessment of clinical history, consensus agreement GBS was primary cause of death. Exclusion criteria: NR. Inclusion / Exclusion (study): Neonatal work stream: 65 infants with GBS infection / 75,791 infants without GBS infection excluded. Pathology work stream: 45 stillbirths related to any infection in 2009 and 2010 / Exclusions NR. Inclusion / Exclusion (analysis): Neonatal work stream: 65 infants with GBS infection / no exclusions. Pathology work stream: 5 stillbirths with GBS infection as the primary cause of death / 40 excluded: 9 infection ascertained as co-factor to cause of death; 13 infection unrelated to cause of death; 18 NR, possibly other infective organisms (not GBS). Inclusion / Exclusion (review questions): 1-6) 43 infants with EOGBS / 22 infants with LOGBS excluded. 7) 23 surviving infants with EOGBS and available information / 42 excluded: 22 LOGBS, 5 died, 15 no available information. 9/10) 5 (as above) / none excluded.
Outcomes	1) Incidence of EOGBS. Case definition EOGBS: GBS-positive blood or CSF culture <7 days. Denominator: Total number of live births in Northern Ireland. 2) Distribution of EOGBS by maternal risk factors. 3) Clinical presentation. 4) Mortality rate. 5) Distribution of EOGBS mortality by maternal risk factors. 6) Short-term morbidities associated with EOGBS. 7) Long-term morbidities. 9) Stillbirths in the UK. 10) Stillbirths by gestational age in the UK.

Ecker 2013[115]	
Methods	Retrospective observational study. Data source: Chart review. Setting: One large, regional, urban tertiary care centre, USA. Study period: 1 January 1990 to 31 December 2007 (18 years).
Population	Inclusion criteria: Infants with positive blood, urine, or CSF cultures for bacteria or fungi at ≤7 days of age from 1 January 1990 to 31 December 2007. Exclusion criteria: If culture was a virus, from an outpatient visit that did not result in a hospital admission, interpreted as a contaminant by the treating physician, infants born outside the study hospital. Inclusion / Exclusion (study): 220 cases of early-neonatal infections / 360 excluded: 2 babies with missing medical records, 20 babies born at outside hospital, 338 babies with cultures determined contaminants. Inclusion / Exclusion (analysis): 220 / none excluded. Inclusion / Exclusion (review questions): 21) 63 with EOGBS / 157 pathogen not GBS.
Exposure	21) 1990-1995 (6 years): no formal IAP guideline followed. 1996-2002 (7 years): IAP primarily risk-factor based (IAP: NR). 2003-2007 (5 years): IAP based on universal GBS screening (IAP: NR).
Outcomes	21) Clinical effectiveness of GBS screening on EOGBS-related mortality and morbidity. EOGBS: Positive blood, urine, or CSF cultures from infants ≤7 days. For infants with more than one early-onset infection episode, only the first episode was considered for analysis.

El Helali 2012[83]	
Methods	Uncontrolled before-and-after study, retrospective data collection. Data source: Data from the medical information department and the microbiology laboratory. All medical records of the newborns with EOGBS and medical records of the mothers were reviewed. Data collection of the characteristics of the mothers was performed using the database of the maternity ward. GBS screening results and incidence of bacteriuria during current pregnancy were collected from laboratory software. Setting: Paris-Saint Joseph hospital, Paris, France. Study period: 2009-2010.
Population	Inclusion criteria: Term deliveries in 2009 and 2010. Exclusion criteria: Preterm delivery before 37 weeks. Inclusion / Exclusion (study): 5,575 term deliveries corresponding to 5,666 live births / 403 preterm deliveries <37 weeks. Inclusion / Exclusion (analysis): 4,851 term deliveries / 724 excluded: 288 NR; 436 no intrapartum PCR screening. Inclusion / Exclusion (review questions): 19) 277 women with term pregnancies and positive antenatal culture screening / 4,574 excluded: 101 unknown GBS status; 2,095 negative GBS status; 2,378 no antenatal culture screening (2010 strategy).
Exposure	19) 2009: Antenatal vagina culture screening strategy (35-38 weeks, lower vaginal swab, culture medium NR): IAP if antenatal screening was positive or in the case of bacteriuria during the current pregnancy or a previous child with EOGBS. If GBS status is unknown at the time of delivery, a risk-factor assessment (eg, membrane rupture > 12 hours, intrapartum fever higher than 38ºC) is used to determine whether IAP should be administered. IAP: Penicillin G (5 million international units followed by 2.5 million international units every 4 hours until delivery). In case of high anaphylaxis risk, in 2009, clindamycin was used if GBS was susceptible and vancomycine. Received IAP (n=255) versus received no IAP (n=22).
Outcomes	19) Effectiveness of IAP in preventing culture negative / probable EOGBS in screen-detected populations. Proven EOGBS: Positive results of blood or CSF in the presence of clinical signs, biological abnormalities, or both clinical signs and biological abnormalities consistent with sepsis. Probable EOGBS: Positive results of GBS culture of gastric fluid aspiration, deep ear specimen, or both, in the presence of clinical signs, biological abnormalities, or clinical signs and biological abnormalities consistent with sepsis in which the blood, CSF, or blood and CSF cultures were negative. Severe symptoms: Rapid clinical deterioration with respiratory distress or cardiovascular instability leading to an intensive care survey in which the average duration of antibiotic therapy was 10 days (except meningitis). Mildly ill patients: Mild respiratory distress with biological abnormalities consistent with sepsis; they were hospitalized in the neonatal ward unit, where the average duration of antibiotic therapy was 7 days.

Fairlie 2013[84]	
Methods	Secondary analysis of the BirthNet multistate cohort. Data source: Active Bacterial Core (ABC) surveillance conducts active, population-based surveillance for invasive GBS disease. Setting: Delivery hospitals in the surveillance area with 10 or more births per year in 10 U.S. states: California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, Tennessee. Study period: 2003 to 2004; for clindamycin also 1998 and 1999.
Population	Inclusion criteria: Neonates born alive to surveillance-area residents in 2003 and 2004 who delivered at surveillance-area hospitals with 10 births per year or more. For clindamycin effectiveness, live births that occurred in Active Bacterial Core surveillance sites in 1998 and 1999 and received clindamycin for IAP or no IAP. Exclusion criteria: NR. Patient selection for BirthNet cohort: Cases of early-onset, invasive GBS disease were identified by routine population-based surveillance. Additionally, a random sample of live births stratified according to surveillance area, year of birth, and birth hospital was selected from birth certificates in all surveillance sites. Inclusion / Exclusion (study): BirthNet cohort 2003-2004: 7,691 live births; BirthNet cohort 1998-1999: 5,134 (5,144?) live births / exclusions NR. Inclusion / Exclusion (analysis): Secondary analysis of BirthNet cohort: Penicillin/ampicillin ≥ 4 hours, term: 730/7,691 (9.5%) / 6,961 (90.5%) excluded as not 1:1 matched by propensity score. Penicillin/ampicillin ≥ 4 hours, preterm: 252/7,691 (3.3%) / 7,439 (96.7%) excluded as not 1:1 matched by propensity score. Cefazolin: unable to create a propensity score-matched set (0%) Clindamycin: 508/12,825 (4.0%) / 12,317 (96.0%) excluded as not 1:1 matched by propensity score. Penicillin/ampicillin < 2 hours: 436/7,691 (5.7%) / 7,255 (94.3%) excluded as not 1:1 matched by propensity score. Penicillin/ampicillin 2-4 hours: 680/7,691 (8.8%) / 7,011 (91.2%) excluded as not 1:1 matched by propensity score. Inclusion / Exclusion (review questions): 19) As in analysis / none excluded.
Exposure	19) Penicillin/ampicillin (≥ 4 hours, 2-4 hours, <2 hours): n=1,049 (491, 340, 218, respectively). Clindamycin: n=254. No IAP: n=1,303.
Outcomes	19) Effectiveness of IAP in preventing EOGBS related morbidity and mortality in screen-detected populations. EOGBS: Isolation of GBS from a normally sterile site in a liveborn neonate less than 7 days of age.

Horvath 2013[116]	
Methods	Prospective cohort study with historical control group. Data source: Prospective data collection. Setting: Markusovszky Teaching Hospital, Szombathely, Hungary Study period: Present: 1 January 1995 to 31 December 2011 (17 years); Historical cohort: 1 February 1984 to 31 December 1994 (>10 years).
Population	Inclusion criteria: Present: Pregnant women attending the hospital's prenatal clinic from January 1, 1995 to December 31, 2011. Historic: Pregnant women attending the hospital's prenatal clinic from February 1, 1984 to December 31, 1994. Exclusion criteria NR. Inclusion / Exclusion (study): Present: 24,950 women, 25,857 newborns / none excluded. Historical: 19,722 women, 19,722 newborns / Exclusions NR. Inclusion / Exclusion (analysis): as above / none excluded. Inclusion / Exclusion (review questions): 21) As above / none excluded.
Exposure	21) Present cohort (1995-2011): GBS screening between 30 and 32 weeks of pregnancy, swabs from distal vaginal (without speculum placement) and rectum; GBS positive women and women with risk factors for the transmission of EOGBS received IAP. IAP: 2g ampicillin, followed by 1g of ampicillin every 4 hours until delivery. Patients allergic to penicillin received erythromycin or clindamycin intravenously in equivalent dosage. Historical cohort (1984-1994): no GBS screening, no IAP.
Outcomes	21) Clinical effectiveness of GBS screening on EOGBS-related mortality and morbidity, neonatal sepsis and neonatal sepsis-related mortality. Definite EOGBS: Clinical signs of GBS disease and/or if blood, CSF, urine, tracheal aspirate, or lung tissue were found positive for GBS. Probable EOGBS: Clinical signs of GBS disease and at least 1 of the following: increased or decreased blood neutrophil count; high count of immature neutrophils; high immature-to-total neutrophil ratio; and abnormal CSF findings, such as increased protein or decreased glucose levels or pleocytosis.

Kojima 2014[81]	
Methods	Retrospective cohort study. Data source: Medical records. Setting: Yokohama Municipal Citizens Hospital, Yokohama, Japan. Study period: 1 January 2008 to 1 April 2010.
Population	Inclusion criteria: Neonates born to GBS carrier mothers with inadequate (<4 hours) IAP; gestational age ≥35 weeks. Exclusion criteria: Gestational age <35 weeks or major congenital anomalies. Inclusion / Exclusion (study): 69 with inadequate (<4 hours) IAP / 205 excluded: 196 adequate IAP, 9 no IAP. Inclusion / Exclusion (analysis): 69 (as above) / none excluded. Inclusion / Exclusion (review questions): 18, 19) 273 born from mothers colonised with GBS (196 adequate IAP, 69 inadequate IAP, 9 no IAP) / none excluded.
Exposure	18, 19) IAP: Intravenous ampicillin or clindamycin depending on the status of penicillin allergy. Adequate IAP: ≥4 hours prior to delivery (n=196) Inadequate IAP: <4 hours prior to delivery (n=69) No IAP (n=9)
Outcomes	18, 19) Effectiveness of IAP in preventing proven and probable EOGBS in screen-detected populations. Proven EOGBS: Based on either the isolation of GBS from normally sterile sites, including blood and CSF. Probable EOGBS: Clinical signs of infection with colonisation of GBS (positive rectal or throat cultures), as well as laboratory abnormalities.

Kunze 2015[41]	
Methods	Prospective surveillance cohort study including retrospective review of the women's prepartum GBS status. Data sources: Obstetrical charts; neonatal data related to GBS infection from patients' clinical charts; clinical data regarding prepartum screening collected according to a standardized questionnaire; retrieved either from the patient's pregnancy documentation pass record or else by contacting her obstetrician's laboratory by telephone or fax. Setting: Freiburg University Medical Centre, a tertiary care facility in southwestern Germany. Study period: February 2011 to January 2012 (12 months).
Population	Inclusion criteria: Pregnant women presenting for delivery in the obstetrical department. Exclusion criteria NR. Inclusion / Exclusion (study): 937 women agreed to participate / 560 excluded (did not agree to participate?). Inclusion / Exclusion (analysis): GBS transmission: 597 (63.7%) mother-infant pairs / 340 excluded: 304 no antenatal screening; 36 unclear. Antenatal screening: 289 (30.8%) with antenatal screening at 35-37 weeks or ≤5 weeks prior to delivery and intrapartum culture screening ≤ 7 days prior to delivery / 648 excluded: 304 no antenatal screening; 344 reason NR. Optimal antenatal screening: 144 (15.4%) with fully-guideline-compatible antenatal screening (as above and use of recto-vaginal swabs and selective media) and intrapartum culture screening ≤ 7 days prior to delivery / 793 excluded: 304 no antenatal screening; 145 no recto-vaginal swab and/or no selective media; 344 reason NR. Inclusion / Exclusion (review questions): 12, 16, 17a) 289 and 144, respectively (as above) / none excluded.
Index test / Reference standard (16, 17a, 17b)	Index test: Study defined as cultures obtained before 38 weeks. Swab site: Recto-vaginal swabs 420/633 (66.4%); vaginal swab only 211/633 (33.3%); unknown 2 (0.3%); Timing of test: 35-37 weeks 375/633 (59.3%); <35 weeks 211/633 (33.3%); >37 weeks 47/633 (7.4%); Culture medium: Selective broth medium 185/633 (29.2%); selective agar medium 601/633 (94.9%); GBS antigen test 6 (0.9%). Reference standard: 16, 17a) GBS carriage in full term labour: Study defined as cultures obtained within 7 days prior to delivery. Swab site: Recto-vaginal 935/937 (99.8%); vaginal only 2/937 (0.2%). Timing of test: ≤ 7 days 784/937 (83.7%); >7 days 153/937 (16.3%). Culture medium: Selective broth medium 937/937 (100%); selective agar medium 937/937 (100%).
Outcomes	12) Transition of GBS carriage status from third trimester to term. 16) Sensitivity and specificity of selective antenatal culture screening for GBS carriage in full term labour. 17a) Predictive value of selective antenatal culture screening for GBS carriage in full term labour.

Kwatra 2014[42]	
Methods	Prospective cohort study (serotype-specific longitudinal study). Setting: Prenatal community clinics in Soweto, Johannesburg; number of centres NR. Study period: August 2010 to August 2011 (12 months).
Population	Inclusion criteria: HIV-uninfected pregnant women confirmed by HIV ELISA test non-reactivity on enrolment, from 20-25 weeks of gestational age on last menstrual cycle and who consented to study participation. Exclusion criteria: Antibiotic treatment in the previous two weeks, any acute illness, symptomatic vaginal discharge, and a known or suspected condition in which vaginal examinations were contradicted. Inclusion / Exclusion (study): 661 included / 2,252 excluded as not meeting inclusion criteria of gestational age, HIV status and antibiotic use. Inclusion / Exclusion (analysis): 507 (76.7%) participants who completed all 4 study visits / 154 excluded: 4 withdrew consent; 13 lost to follow-up; 86 delivered (premature) baby; 24 relocated to different province; 13 miscarriage or stillbirth; 14 missed one visit. Inclusion / Exclusion (review questions): 12) 507 (as above) / none excluded.
Outcomes	12) Transition of GBS carriage status from third trimester to term. Third trimester screening: 31-35 weeks, recto-vaginal swabs, selective and chromogenic medium. Term screening: 37-40 weeks, recto-vaginal swabs, selective and chromogenic medium.

Lamagni 2013[19]	
Methods	Retrospective chart review, population-based surveillance study. Data sources: Routine laboratory reports of invasive GBS disease submitted by microbiology laboratories across England and Wales to the Health Protection Agency (HPA), alongside serotype results from isolates submitted to the national reference laboratory (HPA Streptococcus and Diphtheria Reference Unit [SDRU]). Setting: England and Wales. Study period: Incidence: 1 January 1991 to 31 December 2010; Serotype distribution: 1 January 1995 to 31 December 2010.
Population	Inclusion criteria: Cases with invasive GBS infection defined as GBS cultured from blood or other normally sterile sites. Also included were nonsterile-site GBS isolates from patients clinically diagnosed with meningitis. Exclusion criteria NR. Inclusion / Exclusion (study): Incidence: 21,386 reported cases of invasive GBS infections between 1991 and 2010 / Exclusions NR. Serotypes: 4,878 submitted to the national reference laboratory between 1995 and 2010 / Exclusions NR. Inclusion / Exclusion (analysis): Incidence: 21,386 (as above) / none excluded. Serotyping: 4,583 / 295 (6%) excluded as non-typable. Inclusion / Exclusion (review questions): 1, 6) Incidence: 4,531 cases with EOGBS (0-6 days) / 16,855 cases excluded: 2,498 with LOGBS (7-90 days); 384 paediatric GBS (91 days-14 years); 13,376 adult disease (≥15 years). 1) Serotypes: 1,215 GBS serotypes from early-onset GBS cases / 3,368 GBS isolates not from early-onset GBS cases excluded.
Outcomes	1) EOGBS incidence; GBS serotypes. 6) Short term morbidities. Proven EOGBS: GBS isolated from blood or other normally sterile sites at 0-6 days of life. Also included were nonsterile-site GBS isolates from patients clinically diagnosed with meningitis. Records were considered to relate to the same episode if specimens were taken within 7 days of each other and merged accordingly to form a single record. Denominator: Live birth registrations for the respective years in which cases were diagnosed were used as denominators for calculating rates in infants.

Le Doare 2016[43]	
Methods	Prospective cohort study. Setting: 2 Government health centres offering antenatal care to women in the Fajara area of costal Gambia. Study period: 1 January 2014 to 31 December 2014 / 15 January 2014 to 31 January 2015 (unclear in publication). Follow-up: Daily until day 6 and then asked to return to clinic when the infant was 60-89 days old for final follow-up visit and vaccinations.
Population	Inclusion criteria: Pregnant women > 18 years who had a negative HIV test and were deemed to be at low risk for pregnancy complications (no evidence of preeclampsia, cardiomyopathy, maternal gestational diabetes, placenta praevia, twin pregnancy). Healthy infants over 32 weeks of gestation assessed using the Ballard score and weighing over 2.5kg were included. Exclusion criteria: Mothers not planning to breastfeed or unable to remain in the Fajara area for the first three months postpartum. Infants with obvious congenital abnormalities or requiring resuscitation at the time of delivery requiring transfer to a neonatal unit. Inclusion / Exclusion (study): 750 mother-baby pairs of 3,661 eligible mothers and infants at birth / 10,767 mother-baby pairs excluded: 8,404 out-of-hospital deliveries; 353 maternal complications; 2,010 neonatal complications; 2,911 eligible but excluded as predefined sample size was reached. Inclusion / Exclusion (analysis): At birth: 750 mother-baby pairs (as above) / none excluded. Inclusion / Exclusion (review questions): 13, 14) 750 mother-baby pairs (as above) / none excluded.
Outcomes	13) Transmission from GBS-positive women at term to baby. 14) Proportion of colonised babies affected by EOGBS. Intrapartum GBS carriage: Recto-vaginal swabs; in labour; selective agar (Todd-Hewitt broth supplemented with colistin and nalidixic acid); negative samples and 5 colonies from positive samples were analysed for GBS DNA by real-time PCR. Neonatal GBS colonisation: Nasopharyngeal and rectal swabs; 4 hours after birth, 6 days and 60-89 days; selective agar (Todd-Hewitt broth supplemented with colistin and nalidixic acid). EOGBS: NR (“One child presenting on day 6 of life with irritability and poor feeding, had a positive CSF culture for GBS…”).

Mackay 2012[44]	
Methods	Prospective cohort study. Setting: 1 tertiary referral centre, Tufts Medical Center, Boston, MA, USA. Study period: March 2007 to January 2008. Follow-up period: 2 hours after initiation of IAP.
Population	Inclusion criteria: Women presenting in to Labor and Delivery at term who are known to be GBS positive based on routine screening, singleton pregnancy, intact membranes, no vaginal bleeding, no evidence of chorioamnionitis and reassuring fetal testing. Exclusion criteria: Women allergic to penicillin, antibiotics for any reason since the antepartum GBS culture as well as those with ruptured membranes. Inclusion / Exclusion (study): 64 women / 16 excluded: 11 Ruptured membranes prior to collection of both GBS cultures; 1 delivery prior to collection of the 2nd GBS culture; 4 incomplete data for other reason. Inclusion / Exclusion (analysis): 61 women / 3 enrolled in error with penicillin allergy (n=1) or antibiotics since prior GBS culture (n=2). Inclusion / Exclusion (review questions): 12, 17a) 61 (as above) / none excluded.
Index test / Reference standard (17a)	Index test: Routine antenatal screening (USA, CDC recommendations?); swab site: NR; 35-37 weeks; culture medium NR. Reference test: Vaginal-rectal swabs; at admission for labour & delivery, prior administration of IAP with penicillin; sheep blood agar with selective GBS broth.
Outcomes	12) Transition of GBS carriage status from third trimester to term. 17a) Predictive value of selective antenatal culture screening for carriage status at term.

Manktelow on behalf of MBRRACE-UK (2016)[38]	
Methods	Retrospective chart review, voluntary surveillance. Data source: Deaths reported to MBRRACE-UK. Setting: UK Study period: 2014 (12 months)
Population	Inclusion criteria: Stillbirth from 24 weeks of gestation and neonatal death within 28 days of birth reported to MBRRACE-UK; born in UK; born 2014; CODAC codes 050 or 051. Exclusion criteria: Termination of pregnancy. Inclusion / Exclusion (study): NR / NR Inclusion / Exclusion (analysis): 31 GBS-related stillbirths and 26 GBS-related neonatal deaths / Exclusions NR. Inclusion / Exclusion (review questions): 4) 17 GBS-related neonatal deaths within 7 days of birth / 9 GBS-related neonatal deaths after 7 days of age. 9/10) 31 GBS-related stillbirths / none excluded.
Outcomes	4) Mortality rate attributable to culture-confirmed EOGBS. 9) Incidence of GBS-related stillbirth in the UK in 2014. Nominator: GBS-related stillbirths after 24 weeks of gestation in 2014. Denominator: Total births or total number of stillbirths in 2014. 10) Association of GBS-related stillbirth with gestational age at birth.

Matsubara 2013[50]	
Methods	Retrospective nationwide questionnaire surveillance on culture-confirmed GBS infections. Data source: Structured survey forms mailed to 498 hospitals. Setting: Hospitals in Japan, nationwide. Study period: 1 January 2004 to 31 December 2010 (7 years).
Population	Inclusion criteria: Cases of culture-confirmed GBS infections between 2004 and 2010 (see below for case definition). Exclusion criteria NR. Inclusion / Exclusion (study): 152 hospitals (88 EOGBS cases, 162 LOGBS cases) / 346 hospitals excluded: did not participate in survey??? Inclusion / Exclusion (analysis): For characteristics of GBS disease: 152 hospitals (88 EOGBS cases, 162 LOGBS cases) / none excluded. Inclusion / Exclusion (review questions): 7, 8) 88 EOGBS cases / 162 LOGBS cases excluded.
Outcomes	7) Long-term morbidities in EOGBS cases. 8) Association between clinical presentation and morbidity outcomes. EOGBS: Laboratory isolation of GBS from a normally sterile site (blood, CSF, or joint aspirate) with any clinical signs at age 0-6 days. Pneumonia: Respiratory distress syndrome with a radiological appearance of streaky opacity or confluent lobar opacification that commonly requires mechanical ventilation in addition to a positive blood culture result. Meningitis: Cases with GBS isolation from both blood and CSF.

Okike 2014[49]	
Methods	Prospective, enhanced, national population-based active surveillance. Data source: Through the British Paediatric Surveillance Unit (BPSU), hospital microbiology laboratory reports, and parental reporting via meningitis support charities. Setting: Population-based, UK and Republic of Ireland. Study period: July 2010 to July 2011 (13 months).
Population	Inclusion criteria: Confirmed, probable and possible cases of bacterial meningitis (see below for case definitions). Exclusion criteria: Infants with an intraventricular shunt device or neural tube defects, not meeting analytical case definition, duplicate reports. Inclusion / Exclusion (study): 364 cases / 504 (58%) excluded: 466 not meeting case definition or duplicates, 38 unable to verify. Inclusion / Exclusion (analysis): 364 (as above) / none excluded. Inclusion / Exclusion (review questions): 1) 52 confirmed or possible cases of early-onset GBS meningitis / 312 excluded: 66 no bacteria identified ("probable" cases); 148 no GBS; 98 late-onset GBS meningitis.
Outcomes	1) Incidence of early-onset GBS meningitis. Nominator: Confirmed or possible cases with early-onset meningitis and GBS as significant pathogen identified. Denominator: Live births in 2010 (after adjustment for the 13-month surveillance period). Live birth data were obtained from ONS, National Records of Scotland (available at: http://www.nrscotland.gov.uk), Northern Ireland Statistics and Research Agency (available at: http://www.nisra.gov.uk), and the Republic of Ireland Central Statistics Office. Early-onset: age 0-6 days. Confirmed bacterial meningitis: Isolation of a significant bacterial pathogen from CSF or blood AND CSF pleocytosis (≥20 cells/mm^3 for babies 0-28 days of age) or post-mortem examination and a bacteria identified from the CSF and/or blood. Probable bacterial meningitis: The presence of clinical signs of meningitis (fever or hypothermia or temperature instability PLUS 1 or more neurological findings, eg. Coma, seizures, neck stiffness, apnea, bulging fontanelle) AND CSF pleocytosis (as defined above) AND where appropriate IV antibiotics are given for > 7 days BUT where no significant pathogen is isolated from blood or CSF. Possible bacterial meningitis: The presence of clinical signs of meningitis as above AND a positive blood culture with a significant pathogen AND where appropriate IV antibiotics are given for > 7 days BUT where no CSF was obtained.

Public Health England 2014[36]	
Methods	Retrospective chart review, voluntary surveillance. Data source: PHE voluntary microbiology surveillance database, LabBase2, extracted on 6 May 2014. Setting: England, Wales and Northern Ireland. Study period: 2009-2013 (5 years) or 2013 (12 months) only.
Population	Inclusion criteria NR. Exclusion criteria NR. Inclusion / Exclusion (study): NR / NR Inclusion / Exclusion (analysis): 445 GBS bacteraemia cases in infants / Exclusions NR. Inclusion / Exclusion (review questions): 1) 278 early-onset GBS bacteraemia cases in 2013 / 167 late-onset GBS bacteraemia cases excluded.
Outcomes	1) Incidence of early-onset GBS bacteraemia in 2013. Nominator: GBS bacteraemia in infants <7 days of age. Denominator: 2013 live births in England, Wales and Northern Ireland (Office for National Statistics, data for Northern Ireland remained provisional at the time of publication).

Public Health England 2015[37]	
Methods	Retrospective chart review, voluntary surveillance. Data source: PHE voluntary surveillance database Second Generation Surveillance System (SGSS). Setting: England, Wales and Northern Ireland. Study period: 2007-2014 (8 years) or 2014 (12 months) only.
Population	Inclusion criteria NR. Exclusion criteria NR. Inclusion / Exclusion (study): NR / NR Inclusion / Exclusion (analysis): 479 GBS bacteraemia cases in infants / Exclusions NR. Inclusion / Exclusion (review questions): 1) 303 early-onset GBS bacteraemia cases in 2014 / 176 late-onset GBS bacteraemia cases excluded.
Outcomes	1) Incidence of early-onset GBS bacteraemia in 2014. Nominator: GBS bacteraemia in infants <7 days of age. Denominator: 2014 live births in England, Wales and Northern Ireland (Office for National Statistics).

Scasso 2015[45]	
Methods	Prospective cohort study. Setting: Pereira Rossell Hospital, Montevideo, Uruguay. Study period: 1 April 2011 to 30 April 2012 (13 months). Follow-up: 2 and 4 hours after initiation of IAP.
Population	Inclusion criteria: GBS carriers in active labour admitted to the study hospital, healthy women, singleton pregnancy of ≥ 37 weeks, GBS positive as diagnosed by recto-vaginal culture between 35 and 37 weeks. Exclusion criteria: Precipitous deliveries in which it was not possible to collect samples after IAP, penicillin allergy, current use of antibiotics, and renal disease. Inclusion / Exclusion (study): 60 women / exclusions NR. Inclusion / Exclusion (analysis): 43 with positive recto-vaginal culture at admission prior to IAP / 17 with negative recto-vaginal culture at admission prior to IAP excluded. Inclusion / Exclusion (review questions): 12 and 17a) 60 (as in study) / none excluded.
Index test / Reference standard (17a)	Index test: 35-37 weeks; recto-vaginal swabs; culture medium NR. Reference standard: on admission for active labour prior IAP initiation; recto-vaginal swabs; selective Todd-Hewitt medium.
Outcomes	12) Transition of GBS carriage status from third trimester to term. 17a) Predictive value of selective antenatal culture screening for carriage status at term.

Szymusik 2014[48]	
Methods	Retrospective cohort study. Data sources: NR (Medical records?) Setting: 1st Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland. Study period: January 2011 to December 2011.
Population	Inclusion criteria: Women who gave birth at the study centre between January and December 2011. Exclusion criteria: NR. Inclusion / Exclusion (study): 1,653 / exclusions NR. Inclusion / Exclusion (analysis): Analysed newborns: 304 GBS-positive women at hospital admission; successful retrieval of data concerning newborns in 232 cases / 1,421 excluded: 1,349 GBS-negative mothers at hospital admission, 72 no newborn data. For test accuracy: NR Inclusion / Exclusion (review questions): 12, 16, 17a) as in study analysis (but NR) / none excluded.
Index test / Reference standard (16, 17a)	Index test: 35-37 weeks; NR (possibly recto-vaginal swabs as following revised 2002 CDC guidelines[78]); culture medium NR (possibly selective culture as following revised 2002 CDC guidelines). Reference standard: on admission for labour; swab site NR; culture medium NR.
Outcomes	12) Transition of GBS carriage status from third trimester to term. 16) Sensitivity and specificity of selective antenatal culture screening. 17a) Predictive value of selective antenatal culture screening for carriage status at term.

Turrentine 2013[82]	
Methods	Retrospective cohort study. Data sources: Medical records. Setting: Woman's Hospital of Texas (community hospital), Houston, TX, USA. Study period: 1 January 2003 to 31 December 2007 (5 years)
Population	Inclusion criteria: Women undergoing IAP for GBS colonisation with singleton live births with planned vaginal delivery at ≥37 0/7 weeks of gestation. Exclusion criteria: Scheduled caesarean delivery or the development of chorioamnionitis. Inclusion / Exclusion (study): 4,782 women receiving IAP for GBS colonisation with singleton live birth at ≥37 weeks / 568 excluded: 548 GBS negative; 20 chorioamnionitis. Inclusion / Exclusion (analysis): 4,782 women (as above) / none excluded. Inclusion / Exclusion (review questions): 18, 19) 4,782 women (as above) / none excluded.
Exposure	18, 19) IAP: Penicillin 84.9%; Cefazolin 5%; Ampicillin 4%; Clindamycin 3%; Vancomycin 1%; Erythromycin 0.02%; Other 2%. Study group: IAP <4 hours (n=1,149); control group: adequate IAP ≥ 4 hours (n=3,633). Secondary analysis: IAP <2 hours (n=385); IAP 2 to <4 hours (n=764); IAP ≥4 hours (n=3,633).
Outcomes	18, 19) Effectiveness of IAP in preventing proven and probable EOGBS in screen-detected populations. Suspected GBS infection: Two or more clinical signs of infection but negative cultures from a sterile site, and their mothers had positive intrapartum culture results for GBS. Early-onset sepsis: Positive blood or cerebral spinal fluid culture result and clinical signs of infection. Bacteraemia: Positive blood culture result and no clinical signs of infection. Clinical signs of early-onset sepsis: Fever (>38.0°C); hypothermia (<36.5°C); lethargy; tachypnea (respiratory rate > 60 breaths per minute); apnea (cessation of respiration for >20 seconds); bradycardia (<100 beats per minute); cyanosis; and hypoglycemia (glucose <60 mg/dL and not due to other diagnosis). Clinical sepsis: Total number of infants that were septic and/or had a clinically suspected GBS infection.

Williams 2013[51]	
Methods	Population based survey, retrospective review of infant deaths from infection. Data source: Perinatal Mortality Survey (PMS) database, coordinated by the Regional Maternity Survey Office (RMSO) in the North of England. Setting: North of England (North East and North Cumbria). Study period: 1998-2008 (21 years), three 7-year epochs: 1988-1994, 1995-2001, 2002-2008.
Population	Inclusion criteria: Cases of infant death (0-364 days) from infection: Infection was considered to have contributed to the cause of death when either (i) both a pathological organism was identified and the nature of the death was such that infection was considered to have contributed to that infants demise or (ii) an organism was not identified but infection was considered to be the predominant pathology on the basis of clear clinical findings, where the death could not be attributed to any other condition, and/or where post-mortem histology was supportive. Exclusion criteria: Cases with primary immunodeficiency; cases where infection was not felt likely to be the predominant cause of death (irrespective of whether or not an organism was identified). Inclusion / Exclusion (study): 577 cases with strong evidence that infection was the principal contributor to infant's death / 3,789 cases excluded: 3,298 not involving infection; 491 with infection not the principal contributor to infant's death. Inclusion / Exclusion (analysis): 577 cases (as above) / none excluded. Inclusion / Exclusion (review questions): 4) 64 confirmed GBS deaths in neonatal period (0-27 days) / 513 excluded: 12 confirmed GBS death in post-neonatal period (28-364 days); 13 probable GBS death; 488 other pathogens, not GBS.
Outcomes	4) Mortality rate attributable to culture-confirmed EOGBS. Nominator: Death by confirmed GBS infection. Denominator: Northern Region yearly total livebirth data provided by the Office for National Statistics. Proven EOGBS: GBS isolation from a normally sterile site (blood, CSF or pathological specimens). Probable EOGBS: GBS was only identified from maternal or placental samples, but the clinical presentation was consistent with GBS infection and no other cause of death identified. Early neonatal death: 0-6 days. Late neonatal death: 7-27 days. Early-onset infection: within the first 48 postnatal hours.

Yeung 2014[47]	
Methods	Retrospective cohort study. Data source: Patients' medical notes and institutional computerized obstetric database. Setting: Prince of Wales Hospital, Hong Kong, China. Study period: 1 January 2004 to 31 December 2009 (6 years).
Population	Inclusion criteria: Women having a singleton pregnancy diagnosed with PPROM before 37 weeks of gestation and who delivered between 24 and 36^{+6} weeks from January 1, 2004, to December 31, 2009, in the Prince of Wales Hospital. Exclusion criteria: NR (Multiple births, no PPROM, ROM ≥ 37 weeks, delivery < 37 weeks). Inclusion / Exclusion (study): 680 women confirmed to have PPROM / 36,458 women without PPROM excluded. Inclusion / Exclusion (analysis): 85 women with positive GBS culture on admission / 595 women with negative GBS cultures on admission excluded. Inclusion / Exclusion (review questions): 14) 23 colonised babies without antibiotic prophylaxis / 62 excluded: 38 babies with antibiotic prophylaxis; 24 uncolonised babies without antibiotic prophylaxis.
Outcomes	14) Proportion of colonised babies affected by EOGBS. Neonatal GBS colonisation: GBS culture from either blood, CSF, umbilical cord, ear, eye, or nose without raised C-reactive protein (CRP) >10 in the first 7 days of life. EOGBS: Positive GBS culture from either blood, CSF, umbilical cord, ear, eye, or nose together with raised C-reactive protein (CRP) >10 in the first 7 days of life.

Zuppa 2014[77]	
Methods	Prospective cohort study. Setting: A. Gemelli University Hospital, Rome, Italy. Study period: May 2006 and December 2009. Follow-up: Neonates born to GBS colonised mothers for 48-72 hours.
Population	Inclusion criteria: Mothers and their newborns admitted to the A. Gemelli University Hospital between May 2006 and December 2009, mothers with positive GBS-culture or unknown GBS status and one or more risk factors [prematurity (gestational age < 37 weeks); prolonged rupture of membranes ≥ 18 h; maternal temperature > 38°C in labour]. Exclusion criteria: Mothers with negative GBS-culture or mothers with unknown GBS status without risk factors. Inclusion / Exclusion (study): 1,286 newborns who should have been subjected to IAP / 10,859 screened GBS-negative or were newborns of mothers with unknown GBS status without risk factors. Inclusion / Exclusion (analysis): 854 newborns (676 newborns of GBS colonised mothers eligible for IAP, 178 newborns of mothers with unknown GBS status in presence of risk factor) / 432 GBS colonised mothers with elective caesarean section excluded. Inclusion / Exclusion (review questions): 17b) 53 mother with positive GBS-culture and no IAP / 801 excluded: 178 mothers with unknown GBS status; 623 GBS colonised mothers with IAP. 18) 676 mothers with positive GBS-culture and planned vaginal delivery / 178 mothers with unknown GBS status excluded.
Index test / reference standard (17b)	Index test: 35-37 weeks, recto-vaginal swabs, culture medium NR but followed 2002 CDC guidelines.[78] Reference standard: Presence EOGBS (invasive GBS infection): Blood culture and/or urine culture and/or CSF culture and/or bronchoalveolar fluid positive for GBS. Absence EOGBS (Healthy newborn): 1. The asymptomatic newborn ≥35 weeks subjected to the diagnostic tests provided by the protocol with negative results and clinical observation for 48-72 hours. 2. The asymptomatic newborn <35 weeks subjected to the diagnostic tests provided by the protocol, with negative results, but who still received an empirical antibiotic prophylaxis pending the outcome of the diagnostic tests. Unclear how many of the 53 included neonates were born <35 weeks and received antibiotic prophylaxis.
Exposure	18) Appropriate: IAP at least 4 hours before delivery (n=414). Inappropriate: <4 hours before delivery (n=209). No IAP (n=53).
Outcomes	17b) Predictive value of selective antenatal culture screening for EOGBS disease. 18) Effectiveness of IAP in preventing EOGBS related morbidity and mortality in screen-detected populations.

Appendix 13. Incidence EOGBS disease and EOGBS serotype distribution in the UK (question 1)

Study reference	Area & time period	Population size / Denominator	Number of identified cases / Serotypes	Incidence per 1,000 live births (95% CI)	Notes
BPSU 2016[39]	England Wales Scotland Northern Ireland Republic of Ireland Total April 2014 to April 2015 inclusive (13 months)	716,830 36,339 61,452 26,427 73,084 914,132 live births	421 17 30 17 33 518 Serotype distribution (n=229; 44%) Ia 19.7% (n=45) Ib 7.0% (n=16) II 7.4% (n=17) III 50.7% (n=116) IV 2.6% (n=6) V 7.9% (n=18) VI 0.87% (n=2) VII 0.44% (n=1) VIII 0.44% (n=1) Non-typable 2.6% (n=6)	0.59 (0.53-0.65) 0.47 (0.27-0.75) 0.49 (0.33-0.70) 0.64 (0.38-1.03) 0.45 (0.31-0.63) 0.57 (0.52-0.62)	Culture confirmed EOGBS: Isolation of GBS from a normally sterile site at 0-6 days after birth. Preliminary data. Only 229 of 518 (44.2%) GBS isolates submitted for serotyping.
Eastwood 2014[46]	Northern Ireland 2008 to 2010 inclusive (3 years)	75,856 live births	43 41* Serotypes NR	0.57 0.54*	Culture-confirmed EOGBS. * Exclusion of 2 cases in which additional organisms were grown on blood culture suggesting skin contamination.
Lamagni 2013[19]	England & Wales Incidence: 1 January 1991 to 31 December 2010 (20 years). Serotype distribution: 1 January 1995 to 31 December 2010 (16 years).	NR	4,531 [1991-2010] Serotype distributions (n=1,215) [1995-2010] III 41% Ia 26% V 12% II 9% Ib 8% IV 1%	2000: 0.28 2010: 0.41 Over 20 years, slight increase averaging at 1% per year in EOGBS cases (RR = 1.01, 95% CI, 1.00-1.01). 2005-2010: increase by 5% per annum (RR = 1.05, 95% CI, 1.02–1.08).	Culture-confirmed EOGBS and nonsterile-site GBS isolates from patients clinically diagnosed with meningitis. Improved reporting completeness: 75% in 2003, 83% in 2010.[1] Isolates submitted for serotyping from patients of all ages but with moderate overrepresentation of infant cases (55%) compared to national surveillance data (33%) from this period.

Study reference	Area & time period	Population size / Denominator	Number of identified cases / Serotypes	Incidence per 1,000 live births (95% CI)	Notes
Okike 2014[49]	UK and Republic of Ireland July 2010 to July 2011 (13 months)	954,189 live births	52 Serotypes NR	*0.054*	Inclusion of proven and possible cases of early-onset GBS meningitis. Estimates are likely to represent a minimum incidence because of the strict case definitions and possible underreporting.
Public Health England 2014[36]	England, Wales and Northern Ireland 2013 (12 months)	Number NR 2013 live births in England, Wales and NI (ONS)	UK: 278 England: 257 NI: 12 Wales: 9 Serotypes NR	UK: 0.38 (0.34-0.43) England: 0.39 (0.34-0.44) NI: 0.49 (0.26-0.86) Wales: 0.27 (0.12-0.51)	GBS bacteraemia in infants <7 days. Live birth data for NI provisional at the time of publication. Voluntary surveillance data for 2013, about 85% ascertainment.
Public Health England 2015[37]	England, Wales and Northern Ireland 2014 (12 months)	Number NR 2014 live births in England, Wales and NI (ONS)	UK: 303 England: 272 NI: 18 Wales: 13 Serotypes NR	UK: 0.42 (0.38-0.47) England: 0.41 (0.36-0.46) NI: 0.74 (0.44-1.17) Wales: 0.39 (0.21-0.66)	GBS bacteraemia in infants <7 days. Data collection based on a voluntary reporting system and as such incidence rates can be affected by completeness of reporting.

BPSU, British Paediatric Surveillance Unit; CI, confidence interval; CSF, cerebrospinal fluid; EOGBS, early-onset neonatal Group B streptococcal disease; GBS, Group B Streptococcus; HPA, Health Protection Agency; HSC, Health and Social Care; IV, intravenous; NI, Northern Ireland; NR, not reported; ONS, Office for National Statistics; PHA, Public Health Agency.

Appendix 14. EOGBS mortality rate in the UK (question 4)

Study reference	Area & time period	Population size	Mortality rate in EOGBS cases	Overall mortality rate attributable to EOGBS in all live born babies	Notes
BPSU 2016[39]	UK and Republic of Ireland April 2014 to April 2015 inclusive (13 months)	914,132 live births	Total EOGBS: 5.2% (27/518) 3/57 (5.3%) with EOGBS meningitis. Preterm neonates <28 weeks: 8*/17* (47.1%) Preterm neonates 28-36 weeks: 7*/77* (9.1%) Term neonates: 9*/321* (2.8%)	*3.0 per 100,000 live births (27/914,132 live births)*	Preliminary data. *415/518 (80%) EOGBS cases (including 24/27 deaths) with information on gestational age at birth?* Case definition: Death in infants with isolation of GBS from a normally sterile site within 7 days after birth.
Eastwood 2014[46]	Northern Ireland 2008 - 2010 inclusive (3 years)	75,856 live births	Total: 5/43 (11.6%)* Preterm neonates <37 weeks: 2/11 (18.2%). Term neonates: 3/32 (9.4%). Directly related to sepsis: 3/43 (7%)	*4.0 per 100,000 live births (3/75,856 live births)*	* 2 infants died for reasons other than sepsis. Case definition: GBS-positive blood or CSF culture < 7 days, death directly attributable to GBS.
Manktelow on behalf of MBRRACE-UK 2016[38]	UK 2014 (12 months)	777,764 live births	NR	GBS main cause: 1.7 per 100,000 live births (13/777,764). GBS associated cause: 0.5 per 100,000 live births (4/777,764). Main + associated: 2.2 per 100,000 live births (17/777,764)	Preliminary data. Case definition: Neonatal death within 7 days; CODAC codes 050 or 051; GBS as primary or associated cause of death as reported to MBRRACE-UK.

Williams 2013[51]	Northern England 1998 - 2008 (21 years)	704,536 live births Northern Region yearly total livebirth data provided by the ONS	NR	Proven early-onset infection 1988-2008: 6.5 per 100,000 live births (95% CI 4.6-8.4). 1995-2001: 9.9 per 100,000 live births (95% CI 5.7-14.0) 2002-2008: 3.6 per 100,000 live births (95% CI 1.1-6.1) (p<0.002 versus previous epoch)	Proven GBS infection: GBS isolation from a normally sterile site (blood, CSF or pathological specimens). Early neonatal death: 0-6 days. Early-onset infection: ≤ 48 postnatal hours.

BPSU, British Paediatric Surveillance Unit; CI, confidence interval; CODAC, Causes of Death and Associated Conditions; CSF, cerebrospinal fluid; EOGBS, early-onset neonatal Group B streptococcal disease; GBS, Group B Streptococcus; MBRRACE-UK, Mothers and Babies: Reducing Risk of through Audits and Confidential Enquiries across the UK; NR, not reported; ONS, Office for National Statistics. *Numbers in italics were calculated by reviewers.*

Appendix 15. Distribution of EOGBS mortality rate by maternal risk factors (question 5)

	All	Born ≥37 weeks of gestation	Born >35 weeks of gestation	Notes
BPSU 2016,[39] UK and Republic of Ireland, April 2014 to April 2015 inclusive (13 months)	≥1 RCOG risk factor: 10/27 (37.0%) ≥1 NICE risk factor: 13/27 *(48.1%)* ROM >18 hours: 6/27 *(22.2%)*	≥1 RCOG risk factor: *3/9 (33.3%)* ≥1 NICE risk factor: *3/9 (33.3%)* ≥1 CDC risk factor: *4/9 (44.4%)* ≥1 RCOG or NICE or CDC risk factor: *4/9 (44.4%)*	≥1 RCOG risk factor: 3/10 *(30.0%)* ≥1 NICE risk factor: 4/10 *(40.0%)* ≥1 CDC risk factor: 5/10 *(50.0%)* ROM >18 hours: 2/10 *(20.0%)* ≥1 RCOG or NICE risk factor or ROM >18 hours: 5/10 *(50.0%)*	Preliminary data.
Eastwood 2014,[46] Northern Ireland, 2008 - 2010 inclusive (3 years)	Maternal risk factors present in all neonatal deaths (3/3, 100%) directly related to sepsis.	NR	NR	

BPSU, British Paediatric Surveillance Unit; CDC, Centers for Disease Control and Prevention; NICE, National Institute for Health and Care Excellence; NR, not reported; RCOG, Royal Society of Obstetrician and Gynaecologists; ROM, rupture of membranes.
Numbers in italics were calculated by reviewers.

Appendix 16. Short-term morbidities in EOGBS in the UK (question 6)

Study reference	Short-term morbidities								Notes
	Sepsis / Bacteraemia [n (%)]		Meningitis [n (%)]		Pneumonia [n (%)]		Other [n (%)]		
BPSU 2016[39] England Scotland Wales Northern Ireland Republic of Ireland April 2014 to April 2015 inclusive (13 months)	Premature 67.1% 66.7% 100% 80% 100% Total 63.1%	Term 60.7% 50% 58.3% 58.3% 69.2%	Premature 7.6% - - 20% - Total 13.2%	Term 16% - - 8.3% 19.2%	Premature 25.3% 33.3% - - - Total 23.7%	Term 23.3% 50% 41.7% 33.3% 11.5%	NR		Preliminary data. Actual numbers / missing data NR.
Lamagni 2013,[19] England & Wales, 1991 - 2010	4,436/4,531 (97.9%) positive blood culture		6% 261/4,531 (5.8%) positive CSF culture; 5/4,531 (0.1%) positive brain/spinal cord culture.		14/4,531 (0.3%) lower respiratory tract culture positive		*36/4,531 (0.8%):* 3/4,531 (0.1%) intravascular line culture positive; 5/4,531 (0.1%) liver or bile culture positive; 28/4,531 (0.6%) Other* sites culture positive.		GBS may have been isolated from >1 source in each patient. Culture-confirmed EOGBS and nonsterile-site GBS isolates from patients clinically diagnosed with meningitis.

BPSU, British Paediatric Surveillance Unit; CSF, cerebrospinal fluid; EOGBS, early-onset neonatal Group B streptococcal disease; GBS, Group B Streptococcus; NR, no reported.

* Other sites include aspirate, biopsy, bone marrow, bone pin/plate, eye, gastrointestinal tract, heart/heart valve/pacemaker, intervertebral disc, kidney, lymph nodes, skin/wound, spleen, umbilicus, and upper respiratory tract.

Numbers in italics were calculated by reviewers.

Appendix 17. Long-term morbidities in EOGBS and its association with clinical presentation (questions 7 and 8)

Study reference	Long-term morbidities	Association between clinical presentation and morbidity outcomes	Notes
BPSU 2016[39] UK and Republic of Ireland, April 2014 to April 2015 inclusive (13 months)	NR	Meningitis: 25.9% poor outcome; 29.8% poor outcome or death. Sepsis: 5.1% poor outcome; 11.4% poor outcome or death. Pneumonia: 2.0% poor outcome; 4.9% poor outcome or death.	Preliminary data. Actual numbers / missing data NR. Definition of "poor outcome" not reported.
Eastwood 2014,[46] Northern Ireland, 2008 - 2010 (3 years)	At last paediatric review: 2/23 (8.7%) abnormal neuro-development. Uncertain if these outcomes are directly related to EOGBS infection or are the results of prematurity.	NR	43 EOGBS cases: 43 (100%) sepsis, 3 of them (7.0%) positive CSF cultures in addition to positive blood cultures. Exclusion of 20/43 (46.5%) EOGBS cases: 5 died, 15 no available information.
Matsubara 2013,[50] Japan, 1 January 2004 to 31 December 2010 (7 years)	12/88 (13.6%) survived with sequelae. *12/76 (15.8%)* of surviving cases had sequelae. Speech or mental delay (n=23), epilepsy (n=13), cerebral palsy (n=9), brain atrophy (n=7), hydrocephalus (n=4), visual impairment (n=3) and deafness (n=2) were documented for EOGBS and LOGBS cases. No separate data for EOGBS. Morbidity rate was not different between preterm and term neonates.	8/24 (33.3%) with meningitis had neurological sequelae. The presentation of shock was highly associated with a fatal outcome (5/9).	88 EOGBS cases: 55 (62.5%) sepsis, 24 (27.3%) meningitis, 9 (10.2%) pneumonia. 12/88 (13.6%) died. Long-term morbidity rate may increase after long-term follow-up because cognitive impairment and subtle neurodevelopmental and behavioral delay may be identified later.

BPSU, British Paediatric Surveillance Unit; CSF, cerebrospinal fluid; EOGBS, early-onset neonatal Group B streptococcal disease; NR, not reported.
Numbers in italics were calculated by reviewers.

Appendix 18. Stillbirths associated with GBS in the UK (question 9)

Study reference	Area & time period	Population size	Case definition	Data source	GBS related stillbirth	Notes
Eastwood 2014[46]	Northern Ireland; 2009 - 2010 inclusive (2 years)	NR	i) Histopathological evidence of inflammation in the placenta or foetal tissues, with or without positive culture; ii) A positive culture of any organism from the baby (usually heart, lung or gastric swabs). Review of cases fulfilling i) or ii) by independent Consultant Obstetrician and Consultant Paediatric Pathologist; assessment of clinical history and consensus agreement whether GBS infection was primary cause of death.	Retrospective assessment of antenatal and intrapartum stillbirths referred for autopsy to the Regional Paediatric Pathology Service	2009: n=3 2010: n=2 *9.9 per 100,000 births (5/50,449 births).* *21.7% (5/23)* of all stillbirths with infection as definite cause of death. *15.6% (5/32)* of all stillbirths with infection as definite cause or co-factor of death.	In Northern Ireland, approximately 55% of stillbirths undergo post-mortem examination.[118] → possible underestimation of GBS disease. * Live birth and stillbirth data for Northern Ireland obtained by reviewers from NISRA website.[73]
Embleton 2001[72] (data taken from a systematic review by Nan et al.[52])	England; 1981 - 1996	631,206 (ONS)	20-42 weeks of gestation at delivery	Autopsy/review of clinical reports	3.6 per 100,000 births (23/631,206 births). 0.6% (23/3,591) of all stillbirths. 15.8% (23/146) of all infection-related stillbirths.	Data taken from a systematic review by Nan et al.[52]
Manktelow on behalf of MBRRACE-UK 2016[38]	UK; 2014 (12 months)	780,979	After 24+0 weeks gestational age at delivery; termination of pregnancy excluded. CODAC codes 050 or 051; Primary cause of death as reported to MBRRACE-UK; Associated cause of death as reported to MBRRACE-UK.	Deaths reported to MBRRACE-UK through online reporting system	GBS main cause: 3.1 per 100,000 births. GBS associated cause: 0.9 per 100,000 births. Main + associated: 4.0 per 100,000 births. 0.96% (31/3,215) of all stillbirths.	Preliminary data.

CODAC, Causes of Death and Associated Conditions; EOGBS, early-onset neonatal Group B streptococcal disease; GBS, Group B Streptococcus; MBRRACE-UK, Mothers and Babies: Reducing Risk of through Audits and Confidential Enquiries across the UK; NR, not reported; ONS, Office for National Statistics.
Numbers in italics were calculated by reviewers.

Appendix 19. Natural history of EOGBS (questions 12-14)

Study reference	Setting & time period	Population	Outcomes		
			12. Transition: GBS carriage status 3rd trimester vs. intrapartum	**13. Transmission: GBS-positive mother at term to baby**	**14. Colonised babies affected by EOGBS**
Berardi 2013[40]	1 tertiary care centre, Italy; Enrolment began 20 July 2008, follow-up completed on 1 June 2010.	Included in study: N=182 mother-baby pairs. Included in analysis for question 14): 16 colonised neonates without IAP.	NA	NA	16 colonised neonates during hospitalisation (12 of which immediate vertical transmission); 1 case of EOGBS → *1:16 (6.25%)*
Kunze 2015[41]	1 tertiary care centre, Freiburg, Germany; February 2011 to January 2012 (12 months)	Included in study: N=937 pregnant women presenting for delivery. Included in analysis: N=144 with antenatal screening at 35-37 weeks or ≤5 weeks prior to delivery, recto-vaginal swabs and selective media and intrapartum culture screening ≤ 7 days prior to delivery.	*10.9% (5/46)* changed from positive at 35-37 weeks to negative at ≤ 7 days prior to delivery. *8.2% (8/98)* changed from negative at 35-37 weeks to positive at ≤ 7 days prior to delivery.	NA as IAP > 10%	NA as no case of EOGBS was noted among the cohort.
Kwatra 2014[42]	Prenatal community clinics in Soweto, Johannesburg, South Africa; August 2010 to August 2011 (12 months)	Included in study: N=661 HIV-uninfected pregnant women. Included in analysis: N=507 who completed all 4 study visits.	32.7% (48/147) changed from positive at 31-35 weeks to negative at 37-40 weeks. 11.7% *(42/360)* changed from negative at 31-35 weeks to positive at 37-40 weeks.	NA	NA

Study reference	Setting & time period	Population	Outcomes		
			12. Transition: GBS carriage status 3rd trimester vs. intrapartum	**13. Transmission: GBS-positive mother at term to baby**	**14. Colonised babies affected by EOGBS**
Le Doare 2016[43]	2 Government health centres offering antenatal care to women in the Fajara area of costal Gambia; 1 January 2014 to 31 December 2014/ 15 January 2014 to 31 January 2015???	Included in study: N=750 mother-baby pairs; HIV-uninfected pregnant women > 18 years, low risk for pregnancy complications, presenting in labour. Healthy infants > 32 weeks of gestation and weighing > 2.5 kg. Included in analysis: n=750 (as above).	NA	146 colonised babies at birth born to 253 colonised mothers: 57.7% transmission.	*1/186 (0.5%)* colonised infants at birth developed EOGBS.
Mackay 2012[44]	1 tertiary referral centre, Boston, USA; March 2007 to January 2008 (9 months)	Included in study: N=64 women with positive antenatal GBS culture, singleton pregnancy, term delivery. Included in analysis: N=61 without penicillin allergy or exposure to antibiotics since prior GBS culture.	*23.0%* (14/61) changed from positive at 35-37 weeks to negative on admission for labour.	NA	NA
Scasso 2015[45]	1 hospital, Montevideo, Uruguay; 1 April 2011 to 30 April 2012 (13 months)	Included in study: N=60 healthy women with singleton pregnancy of ≥ 37 weeks, positive antenatal GBS culture. Included in analysis: N=60 (as above).	*28.3% (17/60)* changed from positive at 35-37 weeks to negative on admission for active labour.	NA	NA

Study reference	Setting & time period	Population	Outcomes		
			12. Transition: GBS carriage status 3rd trimester vs. intrapartum	**13. Transmission: GBS-positive mother at term to baby**	**14. Colonised babies affected by EOGBS**
Szymusik 2014[48]	1st Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland; January 2011 to December 2011 (12 months)	Included in study: N=1,653 women giving birth at the study centre. Included in analysis: NR	*27.2% (82/302)* changed from positive at 35-37 to negative on admission for labour. *5.1% (1-NPV)* changed from negative at 35-37 to positive on admission for labour.	NA	NA
Yeung 2014[47]	Prince of Wales Hospital, Hong Kong, China; 1 January 2004 to 31 December 2009 (6 years)	Included in study: N=680 GBS carriers with PPROM <37 weeks. Included in analysis for question 14): 47 GBS carriers with PPROM without antibiotic prophylaxis.	NA	NA	*26.1% (6/23)* colonised neonates developed EOGBS.

EOGBS, early-onset neonatal Group B streptococcal disease; FN, false negative; GBS, Group B Streptococcus; IAP, intrapartum antibiotic prophylaxis; NA, not applicable; NPV, negative predictive value; NR, not reported; PPROM, preterm prolonged rupture of membranes; TN, true negative.
Numbers in italics were calculated by reviewers.

Appendix 20. Bacterial load and bacterial molecular markers predictive of neonatal GBS colonisation or early-onset disease

Study ID Country	Study Design	Participants	Outcome	Prognostic factor groups	Number without outcome	Number with outcome	Summary measure (95% CI)	Covariates adjusted for
SEROTYPE								
GBS transmission from maternal to neonatal colonisation or EOGBS disease								
Al-Sweih 2005[53] Kuwait	Prospective cohort study	124 women colonised with GBS on vaginal-anorectal swabs in labour (Selective culture)	Neonates colonised with GBS on surface swabs at unspecified time (Selective culture)	Ia Ib II III IV V VI VII VIII NT	6 2 7 22 1 14 9 4 0 15	5 1 3 11 0 13 2 2 0 7	Serotype V versus other serotypes: *RR: 1.51 (0.93-2.45)* Type V versus type III: *RR: 1.44 (0 .78-2.69)*	None
GBS transition from neonatal colonisation to EOGBS disease								
Baker 1973[54] USA	Cohort study comparing neonates with EOGBS disease to neonates with asymptomatic GBS colonisation	66 neonates: 54 asymptomatic neonates colonised with GBS on surface culture at mean age of 13.8 hours (selective culture) 13 neonates with EOGBS disease (one patient in both groups)	EOGBS disease < 10 days	Ia Ib Ic II III	6 3 5 21 19	1 1 1 3 7	Not calculated because of double-counting	None
Baker 1974[68] USA	Cohort study comparing neonates with EOGBS disease to neonates with asymptomatic GBS colonisation	Neonates (numbers unclear): 53 asymptomatic neonates colonised with GBS on surface swabs at <3 days 15 neonates with	EOGBS sepsis (clinical symptoms and pre-mortem blood cultures or post-mortem heart and lung cultures in neonates with	Ia Ib Ic II III NT Ia	11.3%, 6 5.4%, 3 9.3%, 5 38%, 20 36%, 19 0%, 0	Sepsis: 2.2% 4.5% 11.1% 44.4% 33.3% 4.5% Meningitis: 10%	Not calculated as no raw numbers	-

Study ID Country	Study Design	Participants	Outcome	Prognostic factor groups	Number without outcome	Number with outcome	Summary measure (95% CI)	Covariates adjusted for
		EOGBS meningitis Unknown number of neonates with EOGBS sepsis	pneumonia) or meningitis (CSF culture) ≤5 days	Ib Ic II III NT		0% 10% 0% 80% 0%		
Chun 1991[56] USA	Case-controlled study comparing EOGBS disease to neonates with asymptomatic GBS colonisation	121 neonates: 74 asymptomatic neonates colonised with GBS at birth on surface swabs 47 EOGBS sepsis	EOGBS sepsis < 7 days Blood and CSF culture	Ia Ib II III Ia/Ib II/III NT	19 13 18 17 0 1 6	11 8 10 15 1 0 2	See meta-analysis results	None
Embil 1987[69] Canada	Prospective cohort study comparing EOGBS disease to neonates with asymptomatic GBS colonisation	55 strains from 54 neonates: 42 asymptomatic neonates colonised with GBS on surface swabs within 1 hour of birth (selective culture) 12 symptomatic GBS	Symptomatic EOGBS < 3 days	Ia Ib Ic II III NT	9 9 0 10 6 8	3 1 0 2 5 2	See meta-analysis results	None
Fluegge 2011[59] Germany	Cohort study comparing EOGBS disease to neonates with asymptomatic GBS colonisation	142 neonates: 46 non-invasive neonates colonised with GBS on surface culture within 24 hours of birth 96 invasive EOGBS	Invasive EOGBS < 7 days Blood and CSF culture	III Other serotype	30% 70%	58% 42%	P<0.001	-
Madzivhandila [70] 2011 South Africa	Prospective cohort study	525 neonates: 389 neonatal isolates colonised on surface swab shortly after birth (Standard	136 neonatal isolates with EOGBS < 7 days Blood and CSF culture	Ia Ib II III IV V	105 24 47 140 18 50	31 7 7 78 5 8	See meta-analysis results	None

Study ID Country	Study Design	Participants	Outcome	Prognostic factor groups	Number without outcome	Number with outcome	Summary measure (95% CI)	Covariates adjusted for
		culture) 136 neonates with invasive EOGBS		NT	5	0		
SEQUENCE TYPE (ST) OF SEROTYPE III STRAINS								
Fluegge 2011[59] Germany	Cohort study comparing EOGBS disease to neonates with asymptomatic GBS colonisation	142 neonates: 46 non-invasive neonates colonised with GBS on surface culture within 24 hours of birth 96 invasive EOGBS	Invasive EOGBS < 7 days Blood and CSF culture	ST-17 ST-19 ST-23 ST-389 Other ST	11 0 2 22 11	61 18 5 1 11	ST-17 in colonised versus invasive: p<0.001 ST-389 in colonised versus invasive: p< 0.001	-
CLONAL COMPLEX (CC) OF SEROTYPE III STRAINS								
Fluegge 2011[59] Germany	Cohort study comparing EOGBS disease to neonates with asymptomatic GBS colonisation	138 neonates 46 non-invasive neonates colonised with GBS on surface culture within 24 hours of birth 96 invasive EOGBS	Invasive EOGBS < 7 days Blood and CSF culture	1 4 8 17 19 23	2 0 1 14 23 3	0 1 2 64 22 6	-	-
REACTION TO C-PROTEIN								
Chun 1991[56] USA	Case-controlled study comparing EOGBS disease to neonates with asymptomatic GBS colonisation	121 neonates: 74 asymptomatic neonates colonised with GBS at birth on surface swabs 47 EOGBS sepsis	EOGBS sepsis < 7 days Blood and CSF culture	No reaction to C-protein Reaction to C-protein	20 54	6 41	*OR: 1.87 (0.89-3.91)*	None
C PROTEIN ß ANTIGEN GENE								
Chun 1991[56] USA	Case-controlled study comparing	121 neonates: 74 asymptomatic	EOGBS sepsis < 7 days	α β	44 15	28 7	-	-

Study ID Country	Study Design	Participants	Outcome	Prognostic factor groups	Number without outcome	Number with outcome	Summary measure (95% CI)	Covariates adjusted for
	EOGBS disease to neonates with asymptomatic GBS colonisation	neonates colonised with GBS at birth on surface swabs 47 EOGBS sepsis	Blood and CSF culture	γ δ	20 10	15 12		
BACTERIAL LOAD								
Number of positive sites								
Dillon 1987[57] USA	Prospective cohort study	1448 neonates colonised with GBS on surface cultures within 1 hour of birth (Selective culture)	EOGBS < 3 days Symptoms and blood, CSF, urine, and other clinical specimens	Light: 1-2 sites Heavy: 3-4 sites	1041 383	4 20	*RR: 12.97 (4.46- 37.70)*	None
Hoogkamp [61]1982 Netherlands	Prospective cohort study	46 women colonised with GBS on throat, nose, vagina, cervix, rectum, and midstream urine swabs in labour (Selective culture)	Neonates colonised with GBS on surface swab at < 6 hours of birth (Selective swab)	Light: 1 site Heavy 2+ sites	64% 9%	36% 91%	*RR: 2.53 (1.93-3.31) (calculated from %)*	None
Lin 2006[63] USA	Retrospective secondary analysis	1674 neonates colonised with on surface culture with GBS before first bath	EOGBS < 7 days Blood or CSF culture	Light: 1-2 sites Heavy: 3-4 sites		4 per 1000 25 per 1000	P<0.001	None
Pass 1979[71] USA	Prospective cohort study	290 neonates colonised with GBS on surface swabs 1-2 hours after birth (Selective culture)	EOGBS Blood and CSF culture	Light: 1-2 sites Heavy: 3-4 sites	198 84	1 7	*RR: 15.31 (1.91- 122.60)*	None
Number of colony counts per plate								

Study ID Country	Study Design	Participants	Outcome	Prognostic factor groups	Number without outcome	Number with outcome	Summary measure (95% CI)	Covariates adjusted for
Easmon 1985[58] England	Prospective cohort study	140 women colonised with GBS on vaginal swabs in labour (Selective and standard culture)	38 neonates colonised with GBS on surface culture within 24 hours of birth and/or on discharge from hospital (Selective culture)	Presence on enrichment only <10 colonies 10-50 colonies >50 colonies	Numbers unclear	Numbers unclear	-	-
		141 women colonised with GBS on rectal swabs in labour (Selective and standard culture)	39 neonates colonised with GBS on surface culture within 24 hours of birth and/or on discharge from hospital (Selective culture)	As above	Numbers unclear	Numbers unclear	-	-
Hoogkamp [61] 1982 Netherlands	Prospective cohort study	46 women colonised with GBS on throat, nose, vagina, cervix, rectum, and midstream urine swabs in labour (Selective culture)	Neonates colonised with GBS on surface swab at < 6 hours of birth (Selective swab)	Light: <10 colonies Moderate: 10-50 colonies Heavy >50 colonies	70% 50% 13%	30% 50% 87%	Not calculated for light and moderate versus heavy as no raw numbers	None
Gerards 1985[60] Netherlands	Cohort study comparing EOGBS disease to neonates with asymptomatic GBS colonisation	68 neonates: 47 neonates colonised with GBS on surface swabs immediately after admission to NICU	EOGBS < 7 days sepsis symptoms with GBS cultured from normally sterile culture	Light: < Three sites positive that were <10 or 10-50 colonies per plate Moderate: < Three sites positive that were >50 colonies per plate OR ≥ three sites	38 9	2 15	Light versus moderate and heavy: p<0.0005	-

Study ID Country	Study Design	Participants	Outcome	Prognostic factor groups	Number without outcome	Number with outcome	Summary measure (95% CI)	Covariates adjusted for
		(Selective culture) 21 EOGBS		positive that were <10-50 colonies per plate; Heavy: ≥ 3 sites that were >50 colonies per plate	0	4		
		66 neonates: 47 neonates colonised with GBS on surface swabs immediately after admission to NICU (Selective culture) 19 probable sepsis	Probable sepsis symptoms with surface culture but no culture from sterile site	Light (as above) Moderate (as above) Heavy (as above)	38 9 0	4 11 4	Light and moderate versus heavy: *RR: 3.13 (2.06- 4.76)*	None
Colony-forming units (cfu) per ml								
Jones 1984[62] USA	Prospective cohort study	130 women colonised with GBS on vaginal swabs at labour (Selective culture)	Neonates colonised with GBS on surface swabs at unspecified time (Selective culture)	Continuous variable of maternal GBS colonisation from 10^2 to 10^8 colony counts	See text	See text	Correlation between cfu/GBS ml in mothers' vagina and neonates' rectum: P<0.001	-
Jones 1984[62] USA	Prospective cohort study	130 women colonised with GBS on vaginal swabs at labour (Selective culture)	EOGBS – 2 neonates were blood culture positive, Probable EOGBS: 1 had symptoms and surface culture positive	Degree of colonisation	See text	See text	See text	-
Persson 1986[66] Sweden	Secondary analysis combined with a prospective cohort study	64 women colonised with GBs on urine swab in labour	12 neonates colonised with GBS on surface culture < 5 days	Light colonisation: <10^4 cfu/ml in urine Heavy colonisation: ≥10^4 cfu/ml in urine	49 3	6 6	*RR: 6.11 (2.52-14.81)*	None

Study ID Country	Study Design	Participants	Outcome	Prognostic factor groups	Number without outcome	Number with outcome	Summary measure (95% CI)	Covariates adjusted for
		(Selective culture)	(Selective culture)					
Sensini 1997[67] Italy	Prospective cohort study	260 women colonised with GBS on lower vaginal swabs in labour (Selective culture)	108 neonates colonised with GBS on surface culture before first bath (Selective culture)	Light: 10^2-10^5 cfu/ml Heavy: 10^6 or greater	78 74	34 74	*RR: 1.65 (1.19- 2.28)*	None
			1 neonate with EOGBS sepsis < 24 hours Blood culture and sepsis symptoms	Light: (As above) Heavy: (As above)	111 148	1 0	-	-
Other								
Boyer 1983[55] USA	Prospective cohort study	207 women colonised with GBS on vaginal swabs in labour who gave birth to 209 neonates (Selective culture)	Neonates colonised with GBS on surface swabs in the delivery room	Light: Negative Intrapartum vaginal culture but positive postpartum rectal/vaginal culture Moderate: Positive Intrapartum vaginal culture on selective broth enrichment only Heavy: Positive Intrapartum vaginal culture on direct plate as well as enrichment	47* 35 38	10* 10 69	Light and moderate vs. heavy: *RR: 3.29 (2.17- 4.99)*	None
			EOGBS	Light: (As above) Moderate: (As above) Heavy: (As above)	57* 45 103	0 0 4	-	
Morales 1986 USA[65]	Untreated control group of RCT	128 women colonised with GBS at labour identified by a rapid slice coagglutination	59 term neonates colonised with GBS on surface swabs at delivery	Light colonisation: Agglutination with GBS antigens was negative at 5 hours but positive at 20 hours Heavy colonisation:	63 6	35 24	*RR: 2.24 (1.63- 3.09)*	None

Study ID Country	Study Design	Participants	Outcome	Prognostic factor groups	Number without outcome	Number with outcome	Summary measure (95% CI)	Covariates adjusted for
		test on selective vaginal culture		Agglutination with GBS antigens was detectable within 5 hours				
			3 GBS sepsis in term neonates Positive body fluid	Light colonisation: (As above) Heavy colonisation: (As above)	98 27	0 3	-	None
Morales 1987 [64] USA	Prospective cohort study	48 women colonised with GBS at labour identified by latex agglutination on selective vaginal culture	17 preterm neonates colonised with GBS on surface swabs a on admission to NICU	Light colonisation: Positive latex agglutination identification at 20 hours but not at 5 hours Heavy colonisation: Positive latex agglutination identification at 5 hours	28 3	9 8	*RR: 2.99 (1.52-5.87)*	None
		48 women colonised with GBS at labour identified by latex agglutination on selective vaginal culture	13 pre-term neonates with GBS sepsis Blood, CSF, or urine culture, and oropharynx cultures with radiographic and clinical signs of infection	Light colonisation: (As above) Heavy colonisation: (As above)	31 4	6 7	*RR: 3.92 (1.66-9.25)*	None

CI: confidence interval; CSF: cerebrospinal fluid; GBS: group B *streptococcus*; EOGBS: early-onset GBS; NT: non-typeable
*Two extra births: 57 infants from 55 mothers
Numbers in italics were calculated by reviewers.

Appendix 21. Study characteristics and GBS screening methodology for test accuracy studies

Study reference	Country and time period	Study design	Population	Index test (questions 15-17): Antenatal culture screening	Reference standard (question 17a): GBS carriage status at term	Reference standard (question 17b): EOGBS
Berardi 2013[40]	Italy 20 July 2008, follow-up until 1 June 2010	Prospective cohort study	In study: 182 mother-baby pairs. Statistical analysis conducted by reviewers for 17b): 76 women with antenatal screening and no IAP.	Recto-vaginal; 35-37 weeks; selective culture.	NA	All neonates followed up until 8 weeks of age. Reference standard for presence/absence of EOGBS NR.
Kunze 2015[41]	Germany February 2011 to January 2012	Prospective cohort study	In study: 937 women. In analysis: Antenatal screening: 289 women; Optimal antenatal screening: 144 women.	Antenatal screening: 35-37 weeks or ≤5 weeks before delivery; recto-vaginal or vaginal; selective or nonselective culture. Optimal antenatal screening: 35-37 weeks or ≤5 weeks before delivery; recto-vaginal; selective culture.	Recto-vaginal; ≤7 days prior to delivery; selective culture.	NA
Mackay 2012[44]	USA March 2007 to January 2008	Prospective cohort study	In study: 64 women. In analysis: 61 women.	Routine antenatal screening (USA); Swab site NR; 35-37 weeks; culture medium NR.	Recto-vaginal; at admission for labour; selective culture.	NA
Scasso 2015[45]	Uruguay 1 April 2011 to 30 April 2012	Prospective cohort study	In study: 60 women. In analysis: 60 women.	Recto-vaginal; 35-37 weeks; culture medium NR but followed 2010 CDC guidelines.[14]	Recto-vaginal; on admission; selective culture.	NA
Szymusik 2014[48]	Poland January 2011 to December 2011	Retrospective cohort study	In study: 1,635 women. In analysis: NR	Followed revised 2002 CDC guidelines[78]: Swab site NR; 35-37 weeks; culture medium NR.	Swab site NR; On admission; Culture medium NR.	NA

Study reference	Country and time period	Study design	Population	Index test (questions 15-17): Antenatal culture screening	Reference standard (question 17a): GBS carriage status at term	Reference standard (question 17b): EOGBS
Zuppa 2014[77]	Italy May 2006 to December 2009	Prospective cohort study	In study: 1,286 women. In statistical analysis conducted by reviewers for 17b: 53 women with positive GBS-culture and no IAP.	Recto-vaginal swabs; 35-37 weeks; culture medium NR but followed 2002 CDC guidelines.[78]	NA	Invasive GBS infection: Blood culture and/or urine culture and/or CSF culture and/or bronchoalveolar fluid positive for GBS. Absence EOGBS: Diagnostic tests: Blood and urine culture; complete blood count; C-reactive protein. All neonates followed up for 48-72 hours. 1. Asymptomatic newborn ≥35 weeks: Diagnostic tests with negative results and clinical observation for 48-72 hours. 2. Asymptomatic newborn <35 weeks: Diagnostic tests with negative results, but received empirical antibiotic prophylaxis pending the outcome of the diagnostic tests.

CSF, cerebrospinal fluid; EOGBS, early-onset neonatal Group B streptococcal disease; GBS, Group B Streptococcus IAP, intrapartum antibiotic prophylaxis; NA, not applicable; NR, not reported.

Appendix 22. Test accuracy of selective antenatal culture screening for GBS carriage status at term (questions 16 and 17a)

Study, country	2x2 table				Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Notes
	TP	TN	FP	FN					
Kunze 2015,[41] Germany Optimal antenatal screening	41	90	5	8	83.7 *(40.8-97.6)*	91.8* *(65.1-99.5)*	89.1 *(44.4-99.0)*	91.2** *(62.1-98.8)*	* Specificity *94.7%.* ** NPV *91.8%.* Optimal antenatal screening: 35-37 weeks or ≤5 weeks prior to delivery, recto-vaginal swabs and selective culture.
Antenatal screening	44	214	13	18	71.0 *(29.8-93.5)*	94.3 *(73.7-99.0)*	77.2 *(33.0-96.0)*	92.2 *(71.4-98.3)*	Antenatal screening: 35-37 weeks or ≤5 weeks prior to delivery, includes screening using vaginal swabs only or nonselective culture medium.
Mackay 2012,[44] USA	47	NA	14	NA	NA	NA	*77.0* *(64.2-86.5)*	NA	Index test: Routine antenatal screening at 35-37 weeks (USA, so assumed to follow CDC guidelines).
Scasso 2015,[45] Uruguay	43	NA	17	NA	NA	NA	*71.7* *(51.7- 85.8)*	NA	Index test: recto-vaginal swabs at 35-37 weeks, culture medium NR.
Szymusik 2014,[48] Poland	220	NR	*82*	69	76.1 (71.9-79.9)	94 .0 (93.0-94.8)	72.8 (68.8-76.4)	94.9 (94.0-95.7)	Index test: at 35-37 weeks following revised 2002 CDC guidelines.[78] Reference standard: at the time of admission, swab site and culture medium NR.

FN, false negative; FP, false positive; GBS, Group B Streptococcus; NA, not applicable; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; TN, true negative; TP, true positive.

Numbers in italics were calculated by reviewers.

Appendix 23. Predictive value of selective antenatal culture screening for EOGBS disease (question 17b)

Study, country	2x2 table				PPV, % (95% CI)	NPV, % (95% CI)	Notes
	TP	TN	FP	FN			
Berardi 2013,[40] Italy	*1*	*52*	*23*	*0*	*4.2 (0.6-12.8)*	*100 (96.6-100)*	All neonates followed up until 8 weeks of age. Reference standard for presence/absence of EOGBS NR.
Zuppa 2014,[77] Italy	*3*	NA	*50*	NA	*5.7 (0.4-40.0)*	NA	Invasive GBS infection: Blood culture and/or urine culture and/or CSF culture and/or bronchoalveolar fluid positive for GBS. Absence EOGBS: Diagnostic tests: Blood and urine culture; complete blood count; C-reactive protein. All neonates followed up for 48-72 hours. 1. Asymptomatic newborn ≥35 weeks: Diagnostic tests with negative results and clinical observation for 48-72 hours. 2. Asymptomatic newborn <35 weeks: Diagnostic tests with negative results, but received empirical antibiotic prophylaxis pending the outcome of the diagnostic tests. Unclear how many neonates were born <35 weeks and received antibiotic prophylaxis until availability of test results.

CSF, cerebrospinal fluid; EOGBS, early-onset neonatal Group B streptococcal disease; FN, false negative; FP, false positive; GBS, Group B Streptococcus; NA, not applicable; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; TN, true negative; TP, true positive.
Numbers in italics were calculated by reviewers.

Appendix 24. Effectiveness of IAP for GBS positive women, Outcome culture positive EOGBS (question 18)

Study	Cases	Effectiveness	P value	Notes / comments
Berardi 2013, Italy[40] Received IAP No IAP	 *0/54* *1/20 (5%)*	NA	NA	Prospective cohort study, 1 single centre. Statistical analysis of published data calculated by reviewers for review question 18. IAP: Ampicillin. EOGBS definition: NR.
De Luca 2016, Italy[80] IAP ≥ 4 hours IAP < 4 hours No IAP	 *0/47* *1/19 (5.3%)* *0/19*	NA	NA	Prospective cohort study, 1 single centre. Statistical analysis of published data calculated by reviewers for review question 18. IAP: Ampicillin as first-line drug; penicillin-allergic mothers clindamycin or vancomycin intravenously. EOGBS definition: GBS infection occurring during the first week of life. Diagnostic assessment included blood cultures, complete blood counts, chest X-rays, and lumbar punctures.
El Helali 2012, France[83] Received IAP No IAP	EOGBS *0/255* *0/22*	NA	NA	Uncontrolled before-after study, 1 single centre; retrospective data collection. Statistical analysis of published data calculated by reviewers for review question 18. IAP: Intravenous Penicillin G, clindamycin (if GBS susceptible) or vancomycin depending on status of penicillin allergy. Proven EOGBS definition: Positive results of blood or CSF in the presence of clinical signs and/or biological abnormalities consistent with sepsis.

Study	Cases	Effectiveness	P value	Notes / comments
Fairlie 2013, USA[84] Penicillin/ampicillin ≥ 4 hours, term No IAP, term	 2/365 *(0.5%)* 23/365 *(6.3%)*	1-RR (95% CI) 91% (+63% to +98%)	 <0.001	Secondary analysis of BirthNet 2003/2004 multistate cohort (for clindamycin also BirthNet 1998/1999) using 1:1 propensity score matching.
Penicillin/ampicillin ≥ 4 hours, preterm No IAP, preterm	2/126 *(1.6%)* 14/126 *(11.1%)*	86% (+38% to +97%)	0.002	EOGBS definition: Isolation of GBS from a normally sterile site in a liveborn neonate < 7 days of age.
Penicillin/ampicillin ≥ 4 hours No IAP	4/491 *(0.8%)* 37/491 *(7.5%)*	89% (+70% to +96%)	<0.001	Effectiveness as 1-risk ratio (% decrease in risk), in which risk ratio is the rate of disease among women receiving IAP divided by the rate of disease among women receiving no IAP.
Penicillin/ampicillin < 2 hours No IAP	9/218 *(4.1%)* 17/218 *(7.8%)*	47% (-16% to +76%)	0.11	
Penicillin/ampicillin 2-4 hours No IAP	15/340 *(4.4%)* 24/340 *(7.1%)*	38% (-17% to +67%)	0.14	Not all included women GBS positive on antenatal screening. BirthNet cohort included all cases of early-onset, invasive GBS disease identified by routine population-based surveillance and a random sample of live births stratified according to surveillance area.
Clindamycin No IAP	14/259 *(5.4%)* 18/259 *(6.9%)*	22% (-53% to +60%)	0.47	
Kojima 2014, Japan[81] IAP ≥ 4 hours IAP < 4 hours No IAP	EOGBS *0/196* *0/69* *0/9*	NA	NA	Retrospective cohort study, 1 single centre. Statistical analysis of published data calculated by reviewers for review question 18. IAP: Intravenous ampicillin or clindamycin depending on status of penicillin allergy. EOGBS definition: Based on either the isolation of GBS from normally sterile sites, including blood and CSF.

Study	Cases	Effectiveness	P value	Notes / comments
Turrentine 2013, USA[82]	Clinical sepsis*	RR (95% CI)		Retrospective cohort study, 1 single centre.
IAP ≥ 4 hours	15/3,633 (0.4%)	Crude: *0.36*	0.03	IAP: Penicillin 84.9%, cefazolin 5%, ampicillin 4%, clindamycin 3%, vancomycin 1%, erythromycin 0.02%, other 2%.
IAP < 4 hours	13/1,149 (1.1%)	Adjusted**: 0.35 (0.16-0.79)	0.01	
Analysis limited to mothers colonised with GBS by vaginal-rectal culture and urine; n=4,028 (84%):				* Clinical sepsis: Infants who were septic and/or had a clinically suspected GBS infection.
IAP ≥ 4 hours	13/3,111 (0.4%)	Crude: *0.29*	<0.01	Early-onset sepsis: Positive blood or CSF culture result and clinical signs of infection.
IAP < 4 hours	13/917 (1.4%)	Adjusted**: NR		Suspected GBS infection: Two or more clinical signs of infection but negative culture from a sterile site, and their mothers had positive intrapartum culture results for GBS.
Secondary analysis:				
IAP ≥ 4 hours	15/3,633 (0.4%)	1	NA	
IAP 2 to < 4 hours	7/764 (0.9%)	Crude: 2.2 (0.9-5.4)	0.08	** Adjusted by multivariate logistic regression for maternal age and duration of rupture of membranes.
		Adjusted**: 2.1 (0.8-5.5)	0.12	
IAP < 2 hours	6/385 (1.6%)	Crude: 3.8 (1.5-9.7)	0.01	
		Adjusted**: 3.5 (1.3-9.6)	0.02	
Zuppa 2014, Italy[77]	Invasive GBS infection			Prospective cohort study, 1 single centre. Statistical analysis of published data by reviewers for review question 18.
IAP ≥ 4 hours	*0/414*	NA	NA	IAP: NR
IAP < 4 hours	*0/209*			Invasive GBS infection: Blood culture and/or urine culture and/or CSF culture and/or bronchoalveolar fluid positive for GBS.
No IAP	*3/53 (5.7%)*			

CI, confidence interval; CSF, cerebrospinal fluid; EOGBS, early-onset Group B Streptococcus disease; GBS, Group B Streptococcus; IAP, intrapartum antibiotic prophylaxis; NA, not applicable; NR, not reported; RR, risk ratio.
Numbers in italics are calculated by reviewers.

Appendix 25. Effectiveness of IAP for GBS positive women, Outcome culture negative/probable EOGBS (question 19)

Study	Cases	Effectiveness	P value	Notes / comments
El Helali 2012, France[83] Received IAP No IAP	 *5/255 (2.0%)* *1/22 (4.5%)*	 *RR= 0.43* *OR=0.42*	 *p=0.39 using Fisher's Exact Test.*	Uncontrolled before-after study; retrospective data collection. Statistical analysis of published data by reviewers for review question 19. IAP: Penicillin G; in case of high anaphylaxis risk clindamycin if GBS susceptible or vancomycine. Probable EOGBS: Positive results of GBS culture of gastric fluid aspiration and/or deep ear specimen in the presence of clinical signs, and/or biological abnormalities consistent with sepsis in which the blood and/or CSF cultures were negative.
Kojima 2014, Japan[81] IAP ≥ 4 hours IAP < 4 hours No IAP	 *0/196* *3/69 (4.5%)* *0/9*	 NA	 NA	Retrospective cohort study. Statistical analysis of published data by reviewers for review question 19. IAP: Intravenous ampicillin or clindamycin depending on status of penicillin allergy. Probable EOGBS: Clinical signs of infection with colonisation of GBS (positive throat or rectal culture), as well as laboratory abnormalities.

CI, confidence interval; CSF, cerebrospinal fluid; EOGBS, early-onset Group B Streptococcus disease; GBS, Group B Streptococcus; IAP, intrapartum antibiotic prophylaxis; NA, not applicable; NR, not reported; OR, odds ratio; RR, risk ratio.
Numbers in italics are calculated by reviewers.

Appendix 26. Adverse events after IAP (question 20)

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
Aloisio 2014 [86]Italy	Cohort	52 newborns 6-7 days old (26 treatment 26 no treatment)	GBS prophylaxis Intrapartum 2g ampicillin at least 4 h before delivery, followed by 1 g every 4 h until delivery	Gut microbiota – *Escherichia Coli* *Bacteroides fragilis* *Bifidobacterium spp* *Clostridium Difficile* *Lactobacillus* spp	M: 8.18 (R: 4.09-12.70) M: 8.17 (R: 4.68-11.99) M: 5.85 (R: 3.24–7.79) M: 3.89 (R: 3.12–4.80) M: 6.69 (R: 5.40–8.93)	M: 9.03 (R: 5.61-11.78) M: 8.53 (R: 5.22-11.16) M: 7.29 (R: 4.12–10.95) M: 3.70 (R: 2.85–5.46) M: 6.73 (R: 5.45–8.20)	NS NS p=0.001 NS NS	None None None None None
Arboleya 2015[87] Spain	Cohort	27 Preterm infants 2-90 days old (14 treatment, 13 no treatment)	- 1 mother received a single dose of penicillin, and 1 mother received 1 dose of ampicillin every 6 hours for 3 days. 12 mothers received ampicillin plus erythromycin [between 2 and 24 doses of each antibiotic)	Gut microbiota composition of 28 microbial groups	<u>Cluster analysis</u> Day 2: Higher percentage of sequences from *Leuconostaceae* in controls. Day 10: Higher percentage of sequences from *Micrococcaceae* and *Propionibacteriaceae* in controls. Day 30: Higher relative amounts of *Comamonadaceae, Staphylococcaceae*, and unclassified *Bacilli* in controls. Higher *Bifidobacteriaceae*, *Streptococcaceae,* unclassified *Actinobacteria*, and unclassified *Lactobacillales* ($p<0.05$) in controls. Lower percentage of *Enterobacteriaceae* in controls ($p<0.05$) 90 days: Most differences disappeared except in *Ruminococcaceae* microbial group (differences unclear) <u>Quantitative PCR</u>: Day 2 and 10: No significant differences Day 30: Higher amounts of *Staphylococcaceae*, in control. Lower amounts of *Enterobacteriaceae* and total bacteria in control. Day 90: higher amounts of *bifidobacteria* in control.		

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
Arboleya 2016[88] Spain	Cohort (same cohort as above Arboleya 2015 study)	27 Preterm infants 2-90 days old (14 treatment, 13 no treatment) (same cohort as above)	- 1 mother received a single dose of penicillin, and 1 mother received 1 dose of ampicillin every 6 hours for 3 days. 12 mothers received ampicillin plus erythromycin [between 2 and 24 doses of each antibiotic)	Gut microbiota composition	Day 1: no statistically significant differences on the bacterial phyla Day 30: higher relative frequency of *Actinobacteria* phylum ($p< 0.05$) and *Firmicutes* phylum ($p < 0.01$) in controls. Lower frequency of *Proteobacteria* phylum in controls. Higher levels of acetic ($p = 0.075$) and total ($p = 0.060$) short chain fatty acids in controls.			
Ashkenazi-Hoffnung 2011[89] Israel	Case-control	195 newborns 7-90 days old 17 treatment 178 no treatment	GBS prophylaxis 94% ampicillin	Late-onset serious bacterial infections	8	63	OR per dose of IAP: 5.19 (0.01-93.11)	Infant age, Maternal age Birth weight, gestational age, type of delivery, and GBS status had no significant effect Number of doses, time from antibiotic administration to delivery
				Ampicillin resistance	85% = 14.45 (Note: Numbers do not add up - 14 people would be 82% and 15 people would be 88%)	63% = 112	p=0.19	None – "Multivariate logistic regression did not identify any variable that was significantly associated with increased risk of resistance to ampicillin or FGCs"
				First-generation cephalosporin	57% = 9.69 (Note: Numbers do not	26% = 46	p=0.19	None – "Multivariate logistic regression did

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
				resistance	add up - 9 people would be 53% and 10 people would be 59%)			not identify any variable that was significantly associated with increased risk of resistance to ampicillin or FGCs"
				First-generation cephalosporin resistance in urinary tract infection	75% (unable to calculate numbers)	23.5% (unable to calculate numbers)	p=0.04	None
				Ampicillin resistance in *Escherichia coli*	100% (unable to calculate numbers)	54.5% (unable to calculate numbers)	p=0.14	None
				First-generation cephalosporin resistance in *Escherichia coli*	60% (unable to calculate numbers)	22.7% (unable to calculate numbers)	p=0.21	None
				Gentamicin or third generation cephalosporin resistance	0	0	-	-
Balter 2003[100] USA	Retrospective cohort	261 children (81 treatment and 180 no treatment)	GBS prophylaxis (59%) Other reasons (39%) Maternal fever (6%) Antibiotic not reported	5 minute APGAR score	Median: 8 IQR: 8-9	Median: 8 IQR: 8-9	-	None
				Complete blood count	21	17	*RR: 2.75 (2.75 (1.53–4.92)*	None
				Blood culture drawn	10	10	*RR: 2.22 (0.96–5.13)*	None
				Urine culture via catheterisation	2	1	*RR: 4.44 (0.41, 48.32)*	None
				Any urine culture	4	2	*RR: 4.44 (0.83, 23.78)*	None
				Chest radiograph	3	8	*RR: 0.83 (0.23-3.06)*	None

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
				Infant given antibiotics within 7 days	6	8	*RR: 1.67 (0.60, 4.65)*	None
				Infant given intravenous catheter	4	8	*RR: 1.11 (0.34-3.58)*	None
				Infant in NICU	3	7	*RR: 0.95 (0.25-3.59)*	None
				Mechanical ventilation	1	0	-	None
				Supplemental oxygen	5	9	*RR: 1.23 (0.43-3.57)*	None
				Hospitalisation ≥ 48 hours	14	12	*RR: 2.59 (1.26-5.35)*	None
				Hospitalisation > 72 hours	14	17	*RR: 1.83 (0.95-3.53)*	None
				Length of hospitalisation	56.8 hours median	47 hours median	p=0.02	None
Briody 2016[90] USA	Retrospective cohort	165 intrapartum women (73 who received 'appropriate' IAP and 92 who received 'inappropriate' IAP)	GBS prophylaxis Appropriate IAP: Penicillin, Cefazolin Inappropriate IAP: Clindamycin, Erythromycin, Vancomycin	Neonate placed on antibiotics	3	4	*RR: 0.94 (0.22-4.09)*	None
				Hospital stay > 2 days	25	22	*RR: 1.43 (0.88-2.32)*	None
				Hospital stay > 3 days	15	16	*RR: 1.18 (0.63-2.23)*	None
				5 minute APGAR score	M: 9 (R: 5-10)	M: 9 (R: 3-10)	p=0.24	None
				Number of blood cultures performed	M: 2 (SD: 2.7)	M: 9 (SD: 9.9)	p=0.11	None
Corvaglia 2016[91] Italy	Prospective cohort	84 newborns 7-30 days of life (35 treatment,	GBS Prophylaxis Intravenous ampicillin every 4 hours until delivery (first	Gut Microbiota *Bifidobacterium spp* 7 days *Bifidobacterium spp* 30 days	Median: 6.01 (IQR: 5.51–6.98) Median: 8.41 (IQR: 7.71-8.80)	Median: 7.80 (IQR: 6.61–8.26] Median: 8.39 (IQR: 7.96-8.86)	p=0.000 p = 0.363	Feeding

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
		49 no treatment)	dose 2 g, following doses 1 g each)	*Lactobacillus spp* 7 days *Lactobacillus spp* 30 days *Bacteroides fragilis spp* 7 days *Bacteroides fragilis spp* 30 days	Median: 5.56 (IQR: 4.94-6.14) Median: 5.29 (IQR: 4.68-6.01) Median: 7.71 (IQR: 5.80-9.33) Median: 7.36 (IQR 5.80-9.09)	Median: 5.45 (IQR: 4.81-6.14) Median: 5.25 (IQR: 4.60-6.15) Median: 7.75 (IQR: 5.87-9.61) Median: 8.51 (IQR: 5.86-9.37)	p = 0.872 p = 0.932 p > 0.05 p > 0.05	
Cox 1996[101] USA	Randomized controlled trial	78 intrapartum women (39 treatment, 39 on treatment)	Preterm labour 2g ampicillin and 1g sulbactam parenterally every 6 hours for 8 doses, followed by ampicillin-clavunate 250mg orally every 8 hours for 5 days.	Symptomatic vulvovaginitis caused by *Candida albicans*	27	Not stated	-	-
				Pseudo-membranous enterocolitis caused by *Clostridium difficile*	1	Not stated	-	-
Dinsmoor 2005[92] USA	Retrospective cohort	435 mother-infant pairs 0-1 month post partum (173 treatment 262 no treatment)	136 for GBS Prophylaxis. Other mothers received antibiotics for other indications	Neonatal thrush	21	18	OR: 1.87 (0.97-3.63)	None
				Maternal thrush	22	17	OR: 2.1 (1.08-4.08)	None
				Total candidiasis	26	20	OR: 2.14 (1.15-3.97)	None
Glasgow 2005[93] USA	Case-control	182 newborns 7-90 days old (62 treatment 120 no	- Penicillin, ampicillin, or broad spectrum	Late-onset serious bacterial infection	37 Penicillin only: 10/23 Broad-spectrum: 29/39	53 80 61	OR: 1.96 (1.05–3.66) OR: 0.95 (0.37-2.44) OR: 4.95; (2.04–11.98)	Hospital of delivery, maternal chorioamnionitis and breastfeeding

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
		treatment)		Ampicillin resistant late-onset serious bacterial infections	24 Penicillin only: 4/9 Ampicillin only: 12/18 Other IAP: 8/10	13 33 25 29	OR: 5.7 (2.3–14.3) OR: 2.5 (0.6-10.6) OR: 6.2 (1.9-19.7) OR: 12.3 (2.3-65.5)	Hospital of delivery
				Ampicillin resistant UTI infections	Not reported	Not reported	OR: 4.3 (1.6 – 11.7)	Hospital of delivery
				Other serious bacterial infections (meningitis, omphalitis, and bacteraemia without UTI)	Not reported	Not reported	OR: 25 (1.8–346)	Hospital of delivery
Gordon 1995[102] USA	Randomized controlled trial	117 intrapartum women (58 treatment, 59 no treatment)	Preterm labour Ceftizoxime for 5 days or 3 days	Bleeding abnormalities	0	-	-	-
				Clostridium difficile colitis	0	-	-	-
				Multi-resistant bacterial infections	0	-	-	-
Jaureguy 2004[94] France	Prospective cohort	50 newborns 3 days old (25 treatment, 25 no treatment)	GBS Prophylaxis Intravenous 2g amoxicillin at the time of labour and then 1g every 4 h until delivery	Gut microbiota – Number colonised *Enterobacteria* *Enterococci* *Staphylococci* *Bacteroides* *Clostridium* *Bifidobacterium*	 13 15 21 13 3 6	 16 17 22 7 10 12	 *RR: 0.81 (0.50-1.31)* *RR: 0.88 (0.58-1.34)* *RR: 0.95 (0.76-1.19)* *RR: 1.86 (0.89-*	None

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
							3.86) *RR: 0.30 (0.09-0.96)* *RR: 0.50 (0.22-1.12)*	
				Amount of colonisation (Log CFU/g) *Enterobacteria* *Enterococci* *Staphylococci* *Bacteroides* *Clostridium* *Bifidobacterium*	 Median: 8.4 (R: 3.3–9.5) Median 8.3 (R: 3.6–10.3) Median: 6.5 (R: 3.6–8.0) Median: 8.0 (R: 6.3–10.3) Median: 5.3 (R: 4.3–5.8) Median: 8.2 (R: 4.3–9.5)	 Median: 9.2 (R: 3.3–9.8) Median: 7.3 (R: 3.3–9.5) Median: 7.0 (R: 4.0–9.3) Median: 7.9 (R: 3.6–9.6) Median: 6.2 (R: 3.6–8.1) Median: 8.5 (R: 6.9-10.3)	 p= 0.18 p=0.78 p=0.53 p=0.12 p=0.01 p=0.1	None
				Amoxicillin-resistant *enterobacteria*	10	12	*RR: 0.83 (0.44-1.56)*	None
				Amoxicillin-resistant *Escherichia Coli*	6	11	*RR: 0.55 (0.24-1.25)*	None
Kampikaho[95] 1993 Uganda	Quasi-randomised controlled trial	660 intrapartum women (330 treatment, 330 no treatment)	Post-partum infection prevention 1g streptomycin or 0.8MU penicillin	Side effects	0	-	-	None

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
Keettel 1949[104] USA	Controlled trial	895 intrapartum women (465 treatment, 430 no treatment)	Post-partum infection prevention 300,000/600,000 units of penicillin at the indication of labour and then after 24-hour intervals.	Mild urticaria	7	-	-	-
				General urticaria	2 (8-12 days, 600,000 units)	-	-	-
				Local allergic manifestations	5 (900,000 units)	-	-	-
				Abscess formations at site of injections	0	-	-	-
				Discomfort following injections	Relatively uncommon and never severe or persistent	-	-	-
Keettel 1950[103] USA	Controlled trial	773 intrapartum women (382 treatment, 391 no treatment)	Post-partum infection prevention 600,000 units of penicillin at the indication of labour, and then after 24-hour intervals.	General urticaria	1 (8 days)	-	-	-
				Local allergic manifestations	1	-	-	-
				Abscess formations at the site of injections	0	-	-	-
Kenyon 2008[96] UK	Factorial randomised trial	3173 children 0-7 years old (numbers differ for outcomes – see treatment column)	Spontaneous preterm labour 375 mg amoxicillin–clavulanate (n=763), 250 mg erythromycin (n=785), amoxicillin–clavulanate and erythromycin	Mild functional impairment	ERY and AMC: 181/769 ERY: 191/785 AMC: 168/763	151/735	OR: 1.00 (reference category) OR: 1.24 (0.96–1.60) OR: 1.29 (1.00–1.65) OR: 1.10 (0.85–1.42)	Maternal baseline, social class, and other factors
				Moderate functional	ERY and AMC:	77/735	OR: 1.00 (reference	Maternal baseline, social class, and other

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
			(n=796), double placebo (n=735)	impairment	91/769 ERY: 94/785 AMC: 85/763		category) OR: 1.22 (0.88–1.70) OR: 1.24 (0.89–1.72) OR: 1.09 (0.78–1.53)	factors
				Severe functional impairment	ERY and AMC: 53/769 ERY: 48/785 AMC: 46/763	47/735	OR: 1.00 (reference category) OR: 1.17 (0.77–1.77) OR: 1.04 (0.68–1.59) OR: 0.97 (0.63–1.49)	Maternal baseline, social class, and other factors
				Any functional impairment	ERY and AMC: 325/769 ERY: 333/785 AMC: 299/763	275/735	OR: 1.00 (reference category) OR: 1.22 (1.00–1.51) OR: 1.23 (1.00–1.51) OR: 1.08 (0.88–1.33)	Maternal baseline, social class, and other factors
				Three or more abnormal attributes	ERY and AMC: 72/769 ERY: 59/785 AMC: 75/763	74/735	OR: 1.00 (reference category) OR: 0.92 (0.66–1.30) OR: 0.73 (0.51–1.04) OR: 0.97 (0.69–1.37)	Maternal baseline, social class, and other factors

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
				Cerebral palsy	ERY and AMC: 35/769 ERY: 18/785 AMC: 15/763	12/735	OR: 1.00 (reference category) OR: 2.91 (1.50–5.65) OR: 1.42 (0.68–2.98) OR: 1.22 (0.57–2.62)	Maternal baseline, social class, and other factors
			Any erythromycin, 250mg (n=1554), no erythromycin (n=1498)	Functional impairment	None: 896 Mild: 372 Moderate: 185 Severe: 101 Any: 658 Three or more abnormal attributes: 131	None: 924 Mild: 319 Moderate: 162 Severe: 93 Any: 574 Three or more abnormal attributes: 149	OR: 1.00 (reference category) OR: 1.20 (1.01–1.43) OR: 1.18 (0.94–1.48) OR: 1.12 (0.83–1.51) OR: 1.18 (1.02–1.37) OR: 0.83 (0.65–1.07)	Maternal baseline, social class, and other factors
				Behaviour	Emotional symptoms: 327 Conduct problems: 480 Hyperactivity: 424 Peer problems: 405 Prosocial behaviour: 122 Overall difficulties: 384 Impact on	Emotional symptoms: 330 Conduct problems: 420 Hyperactivity: 415 Peer problems: 391 Prosocial behaviour: 99 Overall difficulties: 363 Impact on	OR: 0.94 (0.79–1.12) OR: 1.15 (0.98–1.34) OR: 0.98 (0.84–1.15) OR: 1.00 (0.85–1.17) OR: 1.20 (0.91–1.59) OR: 1.03 (0.87–1.21)	Maternal baseline, social class, and other factors

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
					families: 334	families: 292	OR: 1.13 (0.95–1.35)	
			Any erythromycin, 250mg (n=1611), no erythromycin (n=1562)	Cerebral palsy	53	27	OR: 1.93 (1.21–3.09)	Maternal baseline, social class, and other factors
				Seizures	149	116	OR: 1.27 (0.99–1.64)	Maternal baseline, social class, and other factors
				Seizures on prescribed medication	27	17	OR: 1.55 (0.84–2.85)	Maternal baseline, social class, and other factors
				Hydrocephalus with shunt	2	3	OR: 0.65 (0.11–3.87)	Maternal baseline, social class, and other factors
				ADHD from SDQ or parental report	120	116	OR: 1.0 (0.77–1.31)	Maternal baseline, social class, and other factors
				Other developmental problems	10	15	OR: 0.64 (0.29–1.44)	Maternal baseline, social class, and other factors
				Wheezing in last year	295	295	OR: 0.96 (0.81–1.15)	Maternal baseline, social class, and other factors
				Medication for chest problems in last year	262	280	OR: 0.89 (0.74–1.07)	Maternal baseline, social class, and other factors
				Admission to hospital in last year	243	202	OR: 1.20 (0.98–1.46)	Maternal baseline, social class, and other factors
				Admission for chest problems	32	38	OR: 0.81 (0.51–1.31)	Maternal baseline, social class, and other factors
				Diabetes	0	2	-	

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
				All bowel disorders	64	38	OR: 1.66 (1.10–2.49)	Maternal baseline, social class, and other factors
			Any erythromycin, 250mg (n=2375), no erythromycin (n=2279)	Stillbirths	20	24	OR: 0.80 (0.44-1.45)	Maternal baseline, social class, and other factors
				Deaths in first year	61	41	OR: 1.44 (0.96–2.14)	Maternal baseline, social class, and other factors
				Deaths after first year	5	5	OR: 0.97 (0.28–3.34)	Maternal baseline, social class, and other factors
				Total deaths	86	70	OR: 1.19 (0.86–1.63)	Maternal baseline, social class, and other factors
			Any erythromycin, 250mg (n=1641), no erythromycin (n=1598)	Educational attainment – children failing to achieve level 2 or higher in national curriculum tests	Reading: 377 Writing: 413 Maths: 239	Reading: 367 Writing: 413 Maths: 225	OR: 1.0 (0.96–1.04) OR: 1.0 (0.97–1.04) OR: 0.99 (0.96–1.03)	Maternal baseline, social class, and other factors
			Any amoxicillin–clavulanate, 375 mg (n=1532), no amoxicillin–clavulanate (n=1520)	Functional impairment	None: 908 Mild: 349 Moderate: 176 Severe: 99 Any: 624 Three or more abnormal attributes: 147	None: 912 Mild: 342 Moderate: 171 Severe: 95 Any: 608 Three or more abnormal attributes: 133	OR: 1.00 (reference category) OR: 1.02 (0.86–1.22) OR: 1.03 (0.82–1.30) OR: 1.05 (0.78–1.41) OR: 1.03 (0.89–1.19)	Maternal baseline, social class, and other factors

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
							OR: 1.11 (0.87–1.42)	
				Behaviour	Emotional symptoms: 341 Conduct problems: 454 Hyperactivity: 418 Peer problems: 396 Prosocial behaviour: 112 Overall difficulties: 385 Impact on families: 312	Emotional symptoms: 316 Conduct problems: 446 Hyperactivity: 421 Peer problems: 400 Prosocial behaviour: 109 Overall difficulties: 362 Impact on families: 314	OR: 1·09 (0·92–1·30) OR: 1·01 (0·87–1·18) OR: 0.98 (0.84–1.15) OR: 0·98 (0·83–1·15) OR: 1·02 (0·78–1·34) OR: 1·07 (0·91–1·27) OR: 0·98 (0·82–1·17)	Maternal baseline, social class, and other factors
			Any amoxicillin–clavulanate, 375 mg (n=1587), no amoxicillin–clavulanate (n=1586)	Cerebral palsy	50	30	OR: 1.69 (1.07–2.67)	Maternal baseline, social class, and other factors
				Seizures	144	121	OR: 1.21 (0.94–1.56)	Maternal baseline, social class, and other factors
				Seizures on prescribed medication	22	22	OR: 1.0 (0.55–1.81)	Maternal baseline, social class, and other factors
				Hydrocephalus with shunt	4	1	OR: 4.01 (0.45–35.87)	Maternal baseline, social class, and other factors
				ADHD from SDQ or parental report	128	108	OR: 1.20 (0.92–1.57)	Maternal baseline, social class, and other factors

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
				Other developmental problems	8	17	OR: 0.47 (0.20–1.09)	Maternal baseline, social class, and other factors
				Wheezing in last year	291	299	OR: 0.97 (0.81–1.16)	Maternal baseline, social class, and other factors
				Medication for chest problems in last year	257	285	OR: 0.88 (0.73–1.06)	Maternal baseline, social class, and other factors
				Admission to hospital in last year	220	225	OR: 0.97 (0.80–1.19)	Maternal baseline, social class, and other factors
				Admission for chest problems	33	37	OR: 0.89 (0.55–1.43)	Maternal baseline, social class, and other factors
				Diabetes	2	0	-	
				All bowel disorders	54	48	OR: 1.13 (0.76–1.68)	Maternal baseline, social class, and other factors
			Any amoxicillin–clavulanate, 375mg (n=2304), no amoxicillin–clavulanate (n=2350)	Stillbirths	20	24	OR: 0.85 (0.47–1.54)	Maternal baseline, social class, and other factors
				Deaths in first year	49	53	OR: 0.94 (0.63–1.39)	Maternal baseline, social class, and other factors
				Deaths after first year	6	4	OR: 1.53 (0.43–5.42)	Maternal baseline, social class, and other factors
				Total deaths	75	81	OR: 0.94 (0.68–1.30)	Maternal baseline, social class, and other factors

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
			Any amoxicillin–clavulanate, 375 mg (n=1608), no amoxicillin–clavulanate (n=1631)	Educational attainment – children failing to achieve level 2 or higher in national curriculum tests	Reading: 366 Writing: 395 Maths: 230	Reading: 378 Writing: 431 Maths: 234	OR: 0.99 (0.95–1.03) OR: 0.99 (0.95–1.02) OR: 0.99 (0.95–1.03)	Maternal baseline, social class, and other factors
Keski-Nisula 2013[97] Finland	Prospective cohort	45 mother-infant pairs immediately after birth (17 treatment, 28 no treatment)	Intrapartum antibiotics according to hospital protocol including GBS, PROM, caesarean section, chorioamnionitis Intravenous penicillin or amoxicillin in vaginal deliveries and intravenous second-generation cephalosporins in Caesarean deliveries	Gut microbiota – Lactobacillus-dominant mixed flora transmission	1	13	OR: 0.08 (0.007–0.80)	Fetal sex, maternal smoking during pregnancy, meconium in amniotic fluid, duration of ruptured membranes
Keuchkerian 2005[105] Uruguay	Randomised controlled trial	96 intrapartum women (47 treatment, 49 no treatment)	Preterm labour Amoxicillin 1000 mg sulbactam 500 mg IV every 8 h during the first 48 h and they continued to	Palpitations, flushes, nausea and vomiting	2	0	-	-
				Asymptomatic bacteriuria	0	1	-	-
				Urinary infection	1	0	-	-

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
			receive an oral intake of amoxicillin 250 mg sulbactam 250 mg every 8 h for 5 days					
Lin 2006[63] USA	Retrospective cohort	1594 new-borns (213 treatment, 1378 no treatment)	GBS prophylaxis Penicillin	Respiratory distress	44	95	RR: 2.62 (1.79 – 3.83)	Mother's race, mother's race unknown, age <20 yr, primigravida, fever during labor, cesarean delivery, Medicaid/public assistance and positive prenatal culture for GBS, missing values of rupture of membranes and prenatal cultures the degree of colonisation, gestational age by week, race, insulin requirement during pregnancy, suspected infection during labor, intrauterine catheter, unknown Pitocin use, unknown prenatal GBS culture
				Discharge diagnosis of a respiratory disorder	12	39	*RR: 1.96 (1.04-3.69)*	None
McGregor 1986[106] USA	Randomised controlled trial	58 intrapartum women (29	Preterm labour 21 enteric-coated erythromycin	Withdrawal from study due to nausea/and or	1	1	*RR: 1.00 (0.07-15.24)*	

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
		treatment, 29 no treatment)	tablets over 7 days	vomiting				
Nadiasaukiene 1996[110] Lithuania	Randomised controlled trial	102 (44 treatment, 58 control)	Preterm labour 2 x 5g ampicillin four hours apart or 1 hour before delivery if labour proceeded quickly	No explicitly mentioned adverse events (see appendix 26)	-	-	-	-
Rajaei 2006[107] Iran	Randomised controlled trial	80 Intrapartum women (38 treatment, 42 no treatment)	Preterm labour 400 mg erythromycin every 6 h orally for 10 days.	Side effects: nausea, vomiting, hot flushes, decreased deep tendon reflexes, emotional disturbances or drug intolerance	-	-	No significant difference in side effects	-
Sinha 2003[108] USA	Case-control study	228 newborns (114 cases of non-GBS infection and 114 controls) 0-30 days old - 17 newborns 30-0 days old	GBS prophylaxis Penicillin G (41%= 7 people), ampicillin (41%= 7 people), clindamycin (18%= 3 people)	Bloodstream infection	-	-	RR: 0.20 (0.011-3.6)	Sex and year of birth
				Pneumonia	-	-	RR: 2.5 (0.43-14.0)	Sex and year of birth
				Any infection syndrome	-	-	RR: 1.0 (0.38, 2.9)	Sex and year of birth
Stoll 2002[98] USA	Retrospective cohort study	5447 intrapartum women (3554 treatment,	- Ampicillin (49%), penicillin (14%), and erythromycin (13%)	Early-onset sepsis	63	21	OR: 1.1 (0.6–1.8)	Gestational age, the presence or absence of intrauterine growth restriction, birth weight, race or ethnic group,

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
		1893 no treatment)						and sex
				Escherichia. Coli Sepsis or death			No association was found for any maternal antibiotic (data was not shown).	
		33 infants 28 treatment, 5 no treatment	- Ampicillin	Ampicillin-resistant *Escherichia. Coli*	26	1	p=0.01	
		5447 intrapartum women	- IAP within 72 hours (3399), no IAP within 72 hours (2048) - Ampicillin IAP within 72 hours (2348), no ampicillin IAP within 72 hours (3099)	Early onset sepsis	58	26	OR: 1.0 (0.6–1.6)	Gestational age, the presence or absence of intrauterine growth restriction, birth weight, race or ethnic group, and sex
				Escherichia. Coli sepsis	25	12	p=0.004	NS When gestational age and interval between membrane rupture and delivery adjusted for
Svare 1997[109] Denmark	Randomised controlled trial	110 intrapartum women (59 treatment, 51 placebo)	Preterm labour Ampicillin 2grams intravenously every six hours for 24 hours followed by pivampicillin 500 mg orally every eight hours for seven days, plus	Side effects and allergic reactions (undefined)	4	1	*RR: 3.46 (0.40-29.95)*	None

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
			metronidazole 500 mg intravenously every eight hours for 24 hours followed by metronidazole 400 mg orally every eight hours for seven days					
Wohl 2015[99] USA	Retrospective cohort study	492 children 2 years old (128 treated, 364 no treatment)	- Penicillins (108), macrolides (16), aminoglycosides (3), cephalosporins (1)	Diagnosing atopic dermatitis (AD)	Any IAP 37 IAP 0-4 hours: 9/28 IAP 4-12 hours: 11/53 IAP 12-24 hours: 7/26 IAP >24 hours: 6/11	100 100 100 100 100	RR: 1.03 (0.75–1.41) RR 1.17 (0.66–2.06) RR 0.76 (0.44–1.31) RR 0.98 (0.51–1.89) RR 1.99 (1.13–3.49)	None

M, Mean; R, Range; NS, Not Significant; OR, Odds ratio; PROM, Prolonged rupture of membranes; RR, Relative risk; SD, Standard deviation; AMC, Amoxicillin-clavulanate; ERY, Erythromycin; P, Probability value

Numbers in italics are calculated by reviewers.

Appendix 27. Outcomes that may be due to IAP or due to preterm labour/intrapartum infection

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
Cox 1996[101] USA	Randomized controlled trial	82 new-borns (40 treatment, 42 no treatment)	Preterm labour 2g ampicillin and 1g sulbactam parenterally every 6 hours for 8 doses, followed by ampicillin-clavunate 250mg orally every 8 hours for 5 days.	5 minute APGAR score < 7	1	1	*RR: 1.05 (0.07- 16.23)*	None
				Neonatal ICU days	M: 19 (SEM: 0.2, R: 0-21)	M: 22 (SEM: 0.2, R:-0-27)	NS	None
				Respiratory distress ventilation	8	8	NS (unable to calculate RR as some missing)	None
				Necrotizing enterocolitis	0	1	NS (unable to calculate RR as some missing)	None
				Still birth	0	0	NS (unable to calculate RR as some missing)	None
				Neonatal death	1	0	NS (unable to calculate RR as some missing)	None
Gordon 1995[102] USA	Randomized controlled trial	117 intrapartum women (58 treatment, 59 no treatment)	Preterm labour Ceftizoxime for 5 days or 3 days	Maternal infection	2	3	*RR: 0.68 (0.12- 3.91)*	None
				Neonatal pneumonia	0	0	NS	
				Neonatal sepsis	0	0	NS	
				Neonatal positive cultures	2	2	*RR: 1.02 (0.15-6.98)*	None
Kampikaho 1993[95] Uganda	Quasi-randomised controlled trial	660 intrapartum women (167 streptomycin, 163 penicillin, 330 no treatment)	Post-partum infection prevention 1g streptomycin (n=167) or 0.8MU penicillin (n=163)	Laboratory-confirmed post-partum infection	Streptomycin: 14/167 Penicillin: 15/163	51/330	1.00 (reference category) Streptomycin RR: 0.54 (0.31-0.95) Penicillin RR: 0.60 (0.35-1.03)	None
Keettel	Randomised	895	Post-partum	Peurperium fever	66	89	*RR: 0.69 (0.51-0 92)*	None

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
1949[104] USA	controlled trial	intrapartum women (465 treatment, 430 no treatment)	infection prevention 300,000/600,000 units of penicillin at the indication of labour and then after 24-hour intervals.	Peurperium Endometritis	13	40	*RR: 0.30 (0.16-0.55)*	None
				Peurperium Pyelitis	4	1	*RR: 3.70 (0.42-32.96)*	None
				Peurperium Mastitis	5	3	*RR: 1.54 (0.37-6.41)*	None
				Stillbirths	9	12	*RR: 0.69 (0.30-1.63)*	None
				Neonatal deaths	12	12	*RR: 0.92 (0.42-2.04)*	None
Keettel 1950[103] USA	Controlled trial	773 intrapartum women (382 treatment, 391 no treatment)	Post-partum infection prevention 600,000 units of penicillin at the indication of labour, and then after 24-hour intervals.	Fever	29	61	*RR: 0.49 (0.32-0.74)*	None
				Stillbirth	5	3	*RR: 1.71 (0.41- 7.09)*	None
				Neonatal death	4	2	*RR: 2.05 (0 38-11.11)*	None
Keuchkerian 2005[105] Uruguay	Randomised controlled trial	96 intrapartum women (47 treatment, 49 no treatment)	Preterm labour Amoxicillin 1000 mg sulbactam 500 mg IV every 8 h during the first 48 h and they continued to receive an oral intake of amoxicillin 250 mg sulbactam 250 mg every 8 h for 5 days	1 minute APGAR score < 7	3	2	RR: 1.57 (0 27-8.94)	None
				Respiratory distress syndrome	3	3	RR: 1.04 (0 .22-4.91)	None
				Neonatal sepsis	0	0	-	-
				Fetal death	1	1	RR: 1.04 (0.07-16.19)	
				Neonatal death	0	0	-	-
McGregor 1986[106] USA	Randomised controlled trial	17 intrapartum women (8 treatment, 9 no	Preterm labour 21 enteric-coated erythromycin tablets over 7 days	Maternal days in hospital	M: 6.1 (SD: 4.7, R: 3-15)	M: 6.3 (SD: 6.2, R: 2-18)	NS	-
				Amniotic fluid infection	0	0	-	-
				Maternal febrile	0	0	-	-

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
		treatment)		morbidity				
				Initial requirement of neonate intermediate or intensive care nursery	2	3	*RR: 0.75 (0.16-3.41)*	
				Total days in intermediate or intensive care nursery	9	62	-	-
				Total days in any nursery	M: 3 (SD: 2.1)	M: 9.6 (SD: 13.5)	p=0.08	-
				Neonates treated with antibiotics	0	1	-	-
Nadiasaukiene 1996[110] Lithuania	Randomised controlled trial	102 (44 treatment, 58 control)	Preterm labour 2 x 5g ampicillin four hours apart or 1 hour before delivery if labour proceeded quickly	1 minute APGAR score < 7	26	40	*RR: 0.86 (0.63-1.16)*	None
				Neonate did not survive first week	8	12	*RR: 0.88 (0.39-1.96)*	None
				Neonatal infection	4	38	*RR: 0.14 (0.05-0.36)*	None
				Histological chorioamnionitis	6	28	*RR: 0.28 (0.13-0.62)*	None
				Puerperal uterine infection	8	26	*RR: 0.41 (0.20-0.81)*	None
Rajaei 2006[107] Iran	Randomised controlled trial	80 Intrapartum women (38 treatment, 42 no treatment)	Preterm labour 400 mg erythromycin every 6 h orally for 10 days.	Admission to NICU	14	25	p<0.05 *RR: 0.62 (0.38- 1.01) Risk difference: −22.68% (95% CIs: −44.02- −1.34), and p=0.043*	None
Svare 1997[109] Denmark	Randomised controlled trial	110 intrapartum women (59	Preterm labour Ampicillin 2grams intravenously every	Maternal Chorioamnionitis - endometritis	3	0	-	None

Study ID Country	Study design	Participants	Treatment	Outcome	Results Treatment	Control	Summary measure (95%CI)	Covariates adjusted for
		treatment, 51 no treatment)	six hours for 24 hours followed by pivampicillin 500 mg orally every eight hours for seven days, plus metronidazole 500 mg intravenously every eight hours for 24 hours followed by metronidazole 400 mg orally every eight hours for seven days	5 minute APGAR score < 7	5	1	*RR: 4.32 (0.52-35.79)*	None
				Admission to neonatal department	23/58	32	*RR: 0.63 (0.43-0.93)*	None
				Days in neonatal department	Median: 15.5 (R: 1-60)	Median: 27 (R: 2-121)	-	-
				Oxygen /NCPAP /ventilation	M: 9.7 (SD: 15.7)	MD: 10.8 (SD: 17.2)	-	-
				Neonatal antibiotic days	M: 5.9 (SD: 2.8)	M: 6.6 (SD: 4.2)	-	-
				Meningitis septicemia pneumonia	6/58	11	*RR: 0.48 (0.19- 1.20)*	-

M, Mean; R, Range; IQR, Inter-quartile range; NS, Not Significant; OR, Odds ratio; RR, Relative risk; SEM, Standard error of mean
Numbers in italics are calculated by reviewers.

Appendix 28. Study quality according to untailored QUADAS-2[27] (review questions 16 and 17)

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patients	Index test	Reference standard
Berardi 2013,[40] Reviewer conducted analysis	High	Low	Unclear	High	Unclear	Low	17b) Unclear
Kunze 2015,[41] Optimal antenatal screen	High	Low	Unclear	High	Unclear	Low	17a) High
Mackay 2012[44]	Low	Low	Unclear	Low	Unclear	Unclear	17a) Low
Scasso 2015[45]	Unclear	Low	Unclear	Low	Low	Unclear	17a) Low
Szymusik 2014[48]	Unclear	Low	Unclear	High	Unclear	Unclear	17a) Unclear
Zuppa 2014,[77] Reviewer conducted analysis	Low	Low	High	High	Unclear	Unclear	17b) Unclear

Appendix 29. Study quality according to RoBANS[28] (review questions 18 and 19)

Study	1) Selection of participants / Selection bias	2) Confounding variables / Selection bias	3) Measurement of exposure / Performance bias	4) Blinding / Detection bias	5) Incomplete outcome data / Attrition bias	6) Selective outcome reporting / Reporting bias
Berardi 2013,[40] Reviewer conducted analysis	Low	High	Low	Low	High	NA
De Luca 2016,[80] Reviewer conducted analysis	Low	High	Low	Low	High	NA
El Helali 2012,[83] Reviewer conducted analysis	Low	High	Low	Unclear	Low	NA
Fairlie 2013[84]	High	Low	Low	Low	Low	Low
Kojima 2014,[81] Reviewer conducted analysis	Low	High	Low	High	Low	NA
Turrentine 2013[82]	Low	Unclear	Unclear	High	Low	Unclear
Zuppa 2014,[77] Reviewer conducted analysis	Low	High	Low	High	Low	NA

NA, not applicable.
Statistical analysis of published data performed by the reviewers for UK NSC criterion 9.

Appendix 30. Study quality according to RoBANS[28] (review question 21)

Study	1) Selection of participants / Selection bias	2) Confounding variables / Selection bias	3) Measurement of exposure / Performance bias	4) Blinding / Detection bias	5) Incomplete outcome data / Attrition bias	6) Selective outcome reporting / Reporting bias
Bauserman 2013[114]	High	High	Unclear	Low	High	Unclear
Ecker 2013[115]	High	High	Low	Low	Low	Unclear
Horvath 2013[116]	High	High	Low	Low	Low	Unclear