

Cost-effectiveness of rapid tests and other existing strategies for screening and management of early-onset group B streptococcus during labour

B Kaambwa,^a S Bryan,^b J Gray,^c P Milner,^c J Daniels,^d KS Khan,^e TE Roberts^a

^a Health Economics Unit, Public Health Building, University of Birmingham, UK ^b Centre for Clinical Epidemiology and Evaluation, University of British Columbia, Vancouver, BC, Canada ^c Birmingham Women's Foundation Trust, Birmingham, UK ^d University of Birmingham, Clinical Trials Unit and Unit of Reproduction, Genes and Development, Edgbaston, Birmingham, UK ^e Barts and the London School of Medicine, London, UK

Correspondence: Prof TE Roberts, Health Economics Unit, Public Health Building, University of Birmingham, B15 2TT, UK.
Email t.e.roberts@bham.ac.uk

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Objective To determine the cost-effectiveness of alternative screening and prevention strategies, including rapid intrapartum testing, for prevention of early-onset neonatal group B streptococcus (GBS) infection in the UK.

Design A decision model was developed to investigate the cost-effectiveness of screening and prevention strategies for GBS. A strategy of doing nothing was also considered. Deterministic and probabilistic sensitivity analyses were carried out.

Setting Two large UK based obstetric units.

Participants Test accuracy data were obtained from a primary study of rapid tests at the onset of labour and risk factors from 1400 women.

Main outcome measures Incremental health sector costs per case of early-onset GBS death avoided.

Results Compared with a strategy of do nothing, the incremental cost-effectiveness ratio was £32,000 per Early-Onset GBS Disease

avoided and £427,000 per Early-Onset GBS Death avoided for the strategy of providing routine intrapartum antibiotic prophylaxis to all women without prior screening; Based on their current sensitivity, specificity and cost, screening using rapid tests was dominated by other more cost-effective strategies.

Conclusions The most cost-effective strategy was shown to be the provision of routine intrapartum antibiotic prophylaxis to all women without prior screening but, given broader concerns relating to antibiotic use, this is unlikely to be acceptable. In its absence, intrapartum antibiotic prophylaxis directed by screening with enriched culture becomes cost-effective. The current strategy of risk-factor-based screening is not cost-effective compared with screening based on culture.

Keywords Cost-effectiveness, group B streptococcus, labour, rapid tests.

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Introduction

Early-onset group B streptococcus (EOGBS) disease is the leading cause of serious neonatal sepsis in developed countries, affecting 0.5–3 per 1000 live births.^{1–5} Group B streptococcus (GBS) is an opportunistic pathogen harboured in the vagina or rectum in 14% (10–30%) of women.^{4,6} In certain conditions it can be transmitted to the baby during labour, colonising the baby and leading to invasive disease.^{7–9} The risk of developing EOGBS during labour

among infants born to colonised mothers is approximately 12 per 1000 births.¹⁰ If affected, the case-fatality rate can be anywhere between 8 and 15%.^{4,10,11} For those infants that survive the disease, the health and social care costs for the first 2 years of life have been estimated to be twice as high as those for unaffected infants.⁹

The risk of transmitting GBS to newborns is reduced when intrapartum antibiotic prophylaxis (IAP) is administered to women sufficiently early before the baby is born.^{12,13} However, the optimal screening method for

identifying and appropriately treating women with GBS is the subject of controversy. The UK currently recommends IAP based on the presence of one or more of five risk factors, namely, previous baby affected by GBS; GBS bacteriuria detected during the current pregnancy; preterm labour; prolonged rupture of the membranes; and fever in labour. However, the evidence base for this approach is unclear.^{14–16} Some European countries and other western countries, such as the USA, undertake culture-based screening at 35–37 weeks of gestation from vaginal and rectal swabs but some consider such testing premature because the results risk being invalidated by the onset of labour.^{14,15,17,18} New strategies such as vaccines against GBS are seen as promising.^{16,18}

The development of 'Rapid Tests' has offered the possibility of a definitive screening method that can present the results during labour to inform use of IAP.

We report a model-based economic evaluation using data collected prospectively in a primary study undertaken to compare two rapid-test-based screening and prevention strategies, with both existing and hypothetical strategies for GBS infection. The polymerase chain reaction (PCR) and the optical immunoassay (OIA) were the most promising of the rapid tests identified by a systematic review conducted as part of the study.¹⁹ We carried out a model-based cost-effectiveness analysis from the perspective of the NHS in the UK. The primary outcome is based on the additional cost per case of EOGBS-associated infant death avoided; we also report additional costs per case of EOGBS disease avoided.

Methods

Full details of the primary GBS study are presented in the full *Health Technology Assessment* report.¹¹ Briefly, we approached 4873 pregnant women booked for delivery at one of two large UK participating obstetric departments (Birmingham Women's Hospital and King George Hospital, Essex), for consent to be recruited into the study. Women who agreed in principle to participate at 20–24 weeks of gestation were asked again for consent when they presented at labour or when they were admitted to an antenatal ward for induction of labour, after 24 weeks of gestation. We tested the vaginal and rectal swabs taken from these women using enriched microbiological culture, PCR and OIA. We recorded the time and resource use associated with rapid-test-based screening prospectively as part of the study. The rapid-test results, if known before delivery of the baby, did not alter the course of action in terms of treatment because they were not revealed to midwives and doctors caring for the women. Decisions on prescribing IAP, (intravenous penicillin, 3 g, given as soon as possible after the onset of labour and 1.5 g intravenously

4-hourly until delivery) were therefore based on risk factors as per current RCOG guidelines.¹⁴ Enriched microbiological culture of the vaginal and rectal swabs provided the reference standard for determining the accuracy of the rapid-test-based and risk-factor-based screening strategies. A swab from the neonate was also collected from the external ear canal to determine transmission rates. Cost and resource use associated with both risk-factor-based screening and the culture test were recorded prospectively as part of the study.

Interventions and model structure

The accuracy and costs associated with the screening strategies based on rapid tests, risk factors and prenatal cultures were compared with a number of other potential strategies, including a 'Do Nothing' strategy using a decision tree model. We compared a total of ten alternative strategies and these are listed here.

- 1 Routine untargeted IAP to all—[Treat all].
- 2 No screening and no antibiotic prophylaxis—[Do nothing].
- 3 Microbiological culture of vaginal and rectal swabs taken at 35–37 weeks of gestation—[Culture Test].
- 4 Rapid testing during labour using the PCR—(Rapid Test 1 [PCR]).
- 5 Rapid testing during labour using the OIA—(Rapid Test 2 [OIA]).
- 6 Screening using one or more of five risk factors—[Risk factors].
- 7 Risk Factors and Rapid Test 1 (PCR): women who possess one or more of the five risk factors are further tested for GBS using the PCR test and only treated if the test result is positive—[risk factors +ve PCR+ve].
- 8 No Risk Factors and Rapid Test 1 (PCR): women who possess one or more of the five risk factors are treated with antibiotics but those who do not exhibit any of the risk factors are subjected to a PCR test and treated if the result of this test is positive—[risk factors –ve PCR+ve].
- 9 Risk Factors and Rapid Test 2 (OIA): women who possess one or more of the five risk factors are further tested for GBS using the OIA test and only treated if the test result is positive—[risk factors +ve OIA+ve].
- 10 No Risk Factors and Rapid Test 2 (OIA): women who possess one or more of the five risk factors are treated with antibiotics but those who do not exhibit any of the risk factors are subjected to an OIA test and treated if the result of this test is positive—[risk factors –ve OIA+ve].

We considered a decision tree to be the most appropriate model for this study, given the short-term nature of the decision problem.²⁰ We constructed the model in DATA TREEAGE.²¹ Figure 1 presents a subsection of the main

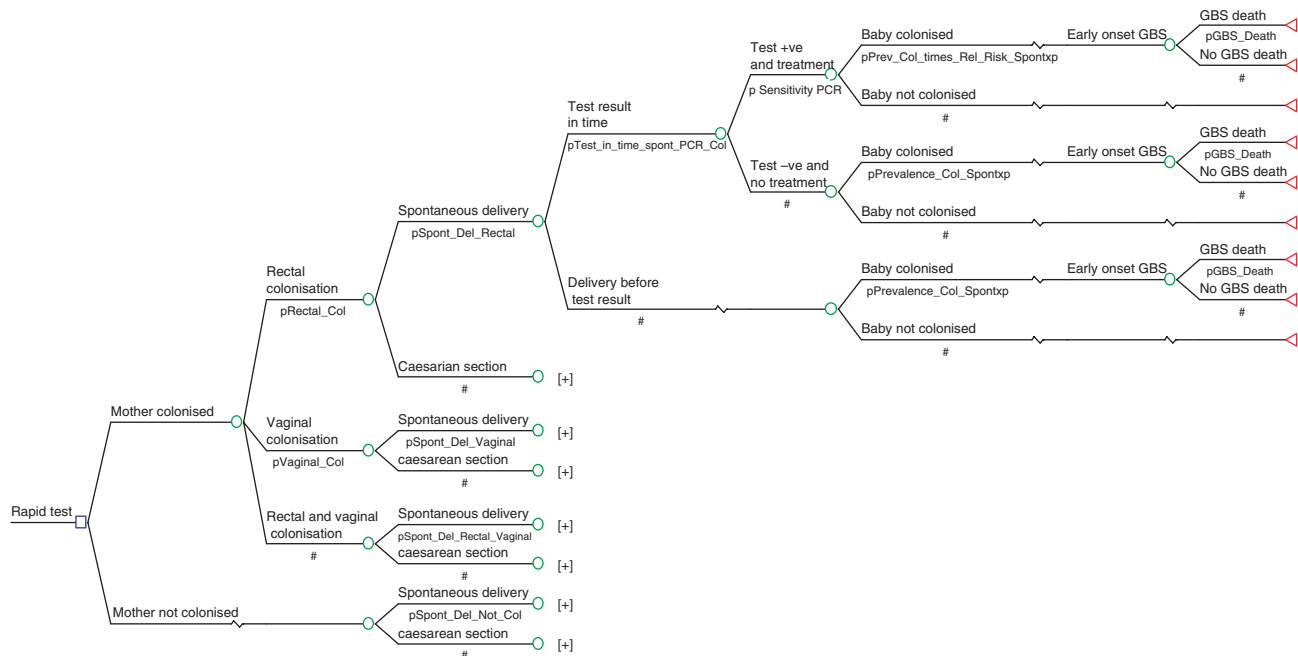


Figure 1. Illustration representing sub-tree 1 or 2; [+] means 'same structure but with appropriate changes in probabilities'. The structure was also adjusted for no-test scenarios. GBS, group B streptococcus.

decision tree and represents strategy 4. Other strategies are analogous but are not presented here because of space constraints and are detailed elsewhere.¹¹ For any given screening strategy, the assumption is that all women presenting in labour are tested for GBS and those who tested positive are treated with antibiotics. In the model, we distinguished between spontaneous and caesarean delivery because the risk of GBS transmission from mother to baby is known to differ by type of delivery.²²

Data sources

Data for the decision tree were collected from the primary study supplemented where necessary from secondary sources.¹¹ We obtained data on maternal colonisation rates from the results of the enriched culture tests performed on all women in the study.¹¹

Estimates of neonatal colonisation rates, incidence of EOGBS disease, treatment effects of maternal antibiotics on EOGBS disease and mortality rates were primarily based on secondary sources.^{12,14,16,23,24}

To calculate the sensitivity and specificity of the rapid tests, we used the results of the enriched culture of combined vaginal and rectal swabs as the reference standard and compared them against those of the rapid tests based on the vaginal swab. For the rapid tests, it was important to ascertain whether or not the test results would be obtained before or after a woman delivered the baby. We determined this through a 'time and motion study' conducted as part of this study.¹¹ We collected unit costs from

various primary and secondary sources.^{11,16,25–28} All cost data are reported in UK£ 2005/06 unit prices and, where appropriate, were discounted at 3.5% as recommended by the UK National Institute for Health and Clinical Excellence (NICE).²⁹

Analysis

We undertook two sets of model-based analyses:

- 1 In Analysis 1, we considered all 10 alternative strategies for identifying and treating women at risk of GBS.
- 2 In Analysis 2, we restricted the analysis to consider only nine strategies and excluded the strategy of routine untargeted IAP.

In the base case for each analysis, the primary outcome was EOGBS-associated infant deaths avoided and we used the case of infant EOGBS disease avoided as the secondary outcome; the test accuracy was determined using the vaginal swab with the combined vaginal and rectal enriched culture as the reference standard; and the Smail odds ratio¹² was used for the effect of maternal antibiotics therapy on EOGBS disease given maternal colonisation.

We undertook the cost-effectiveness analyses using both deterministic and probabilistic approaches.³⁰ Under the former, there is no randomness in the model calculation and during each calculation; each model parameter uses its specified point value.

The following one-way deterministic sensitivity analyses were conducted and were all based on the primary

outcome: (i) Changing the cost associated with EOGBS-associated infant death; (ii) Changing the cost associated with the culture test at 35–37 weeks of gestation; (iii) Changing the estimated effect of IAP on EOGBS disease and death, given maternal colonisation; (iv) Changing the PCR rapid test accuracy from that based on the vaginal swab only to that based on rectal and vaginal swabs combined; (v) Changing the gold standard for determining the accuracy of the OIA and PCR rapid tests from enriched culture of the vaginal and rectal swabs combined to enriched culture of the vaginal swabs only; (vi) Threshold analysis for the cost of rapid PCR testing, to ascertain how low the costs would need to be for the PCR test to become a cost-effective strategy, based on vaginal swabs only; (vii) Threshold analysis for the cost of rapid PCR test, as described in item six, but based on vaginal and rectal swab combined; (viii). Removing the assumption that all women who deliver before the screening test based on culture at 35–37 weeks of gestation, are treated with IAP; (ix) Threshold analysis for the cost of antibiotics (based on vaginal swabs only) as rectal swabs were unacceptable to most women and their midwives.¹¹

A quality-adjusted life-year (QALY) is a measure of health obtained by adjusting a year of life for its quality or value.³¹ There are no available primary studies that have measured the quality of life in children who have experienced and survived EOGBS disease. To be able to compare our primary outcome with the current NICE threshold, we converted incremental cost-effectiveness ratios (ICERs) of EOGBS-associated deaths avoided, to utilities in the following way. We assumed that all infants who avoided death from the disease survived in full health and on the basis that a life in full health, discounted at 3.5%, is worth approximately 27 discounted QALYs,³² we can divide the ICER presented in deaths avoided by 27 QALYs to express the ICER in QALYs. Average life expectancies of 76 and 81 years were assumed for UK males and females, respectively.³²

In interpreting the results of the ICERs, concepts of absolute and extended dominance were used. Under the former, a dominant strategy is one that has greater expected health effectiveness for less or equal expected cost than another, or a strategy that has equal expected health effectiveness for less expected cost than the other.³³ For the latter, the ICER for a given strategy is higher than that of the next, more effective, alternative.³¹ In this case, the index strategy is dominated by a linear combination of two other alternatives as opposed to just one.³⁴

Results

Of the 1400 women recruited into the study, 308 (22.1%) women had risk factors. Over 50% had spontaneous labour and the majority had vaginal delivery (61%). For all

women the length of labour varied from 0.03 to 57.7 hours. Labour was <0.63 hours for 1.06%; <1.3 hours for 4.33%; <3 hours for 18.86%; and <4 hours for 28.21%.

The data on parameters required for the model are presented in Table 1. The overall neonatal colonisation rate was estimated by the primary study to be 0.0921 and this rate was weighted by mode of delivery and maternal colonisation for use in the model. For the incidence of EOGBS disease given neonatal colonisation, we used an estimate of 0.00518, which was determined through a modelling calibration process. The process requires adjustments in the model until the model reproduces the observed incidence of EOGBS disease in the absence of systematic screening or widespread IAP. For the UK this figure is 0.5/1000.¹⁴

The time and motion study (presented in Supporting Information Appendix S1) found that if the time-period between the swab being taken and delivery was at least 80 minutes, then the results from a PCR test would be ready before the woman delivered. The corresponding time for an OIA test was about 37 minutes.¹¹

The estimates of test sensitivity and specificity are presented in Table 2 and a summary of the unit costs used in the model is presented in Table 3. The costs of the PCR and OIA tests, which were estimated as part of the study, were £29.95 and £16.09, respectively.

Analysis 1

The results from the deterministic analyses are almost identical to those from the probabilistic analyses¹¹ and so, in this case, it was considered acceptable to report deterministic results as the primary analysis. The main results for the deterministic analysis for the base-case model are presented in Table 4 and ordered from least costly to most costly strategy. The results show that the 'Do nothing' strategy which implies 'No screening and no IAP for all women' is the least costly strategy but also the least effective. In terms of cost, the average cost per woman for this strategy is UK £1059. Under this strategy of 'Do nothing', approximately 476 per million infants will develop EOGBS, which concurs with the observed population rate in the UK approximated at 0.5 per 1000 women.¹⁴ Of every one million infants born, 36 will die as a result of the disease and 999 964 per million infants will not die (effectiveness 99.9964%).

The ICERs for the strategy of screening based on risk factors compared with a strategy of 'Do nothing' are £50,000 per EOGBS disease avoided and £660,000 per EOGBS death avoided. However, under extended dominance, ICERs of £32,000 per EOGBS disease avoided and £427,000 per EOGBS death avoided, for the strategy of 'Routine untargeted IAP to all' compared with the strategy of 'Do nothing' are more favourable. This strategy would therefore be preferred if the ICERs were deemed to be within an acceptable threshold. When the ICER of £427,000 per EOGBS-associated

Table 1. Model data*

	Maternal colonisation rate (95% CI**)	Prevalence of neonatal colonisation*** (95%CI**)
Maternal colonisation (overall)	0.2128 (0.1916–0.2354)	
Site of colonisation		
Rectal only	0.2746 (0.2244–0.3293)	
Vaginal only	0.0949 (0.0640–0.1342)	
Both rectal and vaginal	0.6305 (0.5726–0.6857)	
Site of colonisation by delivery type		
Rectal only, spontaneous delivery	0.7778 (0.6717–0.8627)	
Rectal only, caesarean delivery	0.2222 (0.1373–0.3283)	
Vaginal only, spontaneous delivery	0.7500 (0.5513–0.8931)	
Vaginal only, caesarean delivery	0.2500 (0.1069–0.4487)	
Both rectal and vaginal, spontaneous delivery	0.7043 (0.6331–0.7688)	
Both rectal and vaginal, caesarean delivery	0.2957 (0.6331–0.7688)	
No maternal colonisation (overall)	0.7872 (0.7646–0.8084)	
Spontaneous delivery	0.7972 (0.7721–0.8207)	0.0099 (0.0031–0.0167)****
Caesarean delivery	0.2028 (0.1792–0.2279)	0.0051 (– 0.0048 to 0.015)****
Incidence of EOGBS disease given neonatal colonisation		0.00518*****
Incidence of EOGBS disease in the absence of systematic screening or widespread IAP		0.0005 (0.5/1000 live births)†
Odds ratio for the effect of maternal antibiotics on EOGBS disease given maternal colonisation ×		0.17††
Odds ratio for the effect of maternal antibiotics on EOGBS disease given maternal colonisation		0.028†††
Mortality rates		
Population infant mortality rate		0.0054††††
Mortality rate in infants with EOGBS disease		0.0800††††
Additional mortality due to EOGBS disease in EOGBS disease population		0.0746‡
Additional mortality due to EOGBS disease in entire population		0.0000373‡‡

*Source is GBS study unless otherwise stated.

**Confidence interval.

***Overall prevalence of neonatal colonisations (95% CI) for both colonised and non-colonised mothers was 0.0921 (0.0043–0.0195).

****Neonatal colonisation may have originated from nosocomial sources or may be linked to mothers with false-negative cultures.

*****This is a calibrated value.

†Source: RCOG.¹⁴

††Source: Smail¹². Referred to as the 'Smail odds ratio' in the text.

†††Source: Colbourn et al.¹⁶. Referred to as the 'Colbourn estimate' in the text and was used in the sensitivity analysis.

††††Source: Office for National Statistics.²³

†††††Source: Weisner et al.²⁴ Infant mortality can be the result of EOGBS disease or other causes.

‡Infant mortality due to EOGBS disease alone. Calculated from inputs a and b.

‡‡Calculated from input c and &.

death avoided is converted to a utility, based on the estimation that a life in full health is worth approximately 27 discounted QALYs, the result is an ICER of approximately £15,815 per QALY (£427,000/27 QALYs).

Analysis 2

When the strategy of providing 'Routine IAP to all' is removed for the purpose of Analysis 2, the ICERs for the

strategy of culture test at 35–37 weeks of gestation, compared with the strategy of risk factors, were £42,000 per disease avoided and £612,000 per infant death avoided (Table 4). Under extended dominance, the comparison of the strategies of culture test at 35–37 weeks of gestation and 'Do nothing' provide slightly more favourable ICERs of £45,000 per disease avoided and £633,000 per death avoided, compared with the strategy of screening based on

Table 2. Sensitivity and specificity of tests*

Test**	Sensitivity*** (95% CI)	Specificity*** (95% CI)	Sensitivity**** (95% CI)	Specificity**** (95% CI)
PCR (Overall)	0.5836 (0.5249–0.6407)	0.9216 (0.8978–0.9414)	0.6981 (0.6315–0.7591)	0.9079 (0.8896–0.9241)
PCR (Given presence of risk factors)	0.697 (0.590–0.790)	0.905 (0.857–0.941)	0.7761 (0.6578–0.8689)	0.8695 (0.8191–0.9102)
PCR (Given absence of risk factors)	0.534 (0.463–0.604)	0.926 (0.906–0.942)	0.6621 (0.5789–0.7385)	0.9171 (0.8972–0.9343)
OIA (Overall)	0.3478 (0.2893–0.410)	0.9178 (0.892–0.9393)	0.4033 (0.3312–0.4786)	0.9090 (0.8896–0.926)
OIA (Given presence of risk factors)	0.474 (0.360–0.591)	0.913 (0.862–0.949)	0.5333 (0.4000–0.6633)	0.9134 (0.8918–0.9318)
OIA (Given absence of risk factors)	0.291 (0.225–0.365)	0.919 (0.897–0.938)	0.3388 (0.2553–0.4305)	0.8939 (0.8461–0.9317)
Culture*****	0.7580 (0.4720–0.9150)	0.9470 (0.8850–0.9850)		
Risk factors	0.3131 (0.2516–0.3798)	0.7979 (0.7738–0.8206)		

*Source is GBS study unless otherwise stated.

**Tests are as defined under 'Interventions and model structure' in the Methods section.

***Enriched culture of the vaginal and rectal swabs provided the gold standard for determining the accuracy of the rapid tests.

****Enriched culture of the vaginal swabs only provided the gold standard for determining the accuracy of the rapid tests.

*****Source: Colbourn *et al.*¹⁶

Table 3. Summary costs per patient for group B streptococcus*

Cost item	Cost (UK £)**	Source***
Tests		
PCR (vaginal or rectal)	29.95	A, B, C, D
OIA (vaginal or rectal)	16.09	A, B, C, D
Culture (mother)	10.63	A, B, C, D
Antibiotics		
Penicillin	14.49	A, C, D, E
Clindamycin	12.17	A, C, D, E
Cost of delivery		
Normal delivery	891.00	F
Caesarean delivery	1643.00	F
Cost of disease		
Mother (cost of treatment)	14.28	A, C, D, E
Baby:		
Early onset GBS—death	5124.90	I
Early onset GBS—no death	8852.07	I
Cost of identifying risk factors (weighted total)	2.96	A, B, C, D

*Full detail of all methods and results carried out as part of the costing analysis are presented in the main report.¹⁵

**Costs have a common price year of 2005/06.

***A, Birmingham Women's Hospital; B, GBS Time and Motion Study; C, Curtis and Netten²⁶; D, NHS²⁵; E, British National Formulary Costs²⁸; F, Department of Health²⁷; I, Colbourn *et al.*¹⁶

risk factors and doing nothing (£50,000 and £660,000, respectively). However, this would only be the preferred strategy if the ICERs of £45,000 per disease avoided and £633,000 per death avoided, were deemed to be within an acceptable threshold. When the £633,000 per death avoided ICER is presented in terms of QALYs, (as per Analysis 1) the estimated cost per QALY is approximately £23,444 per QALY.

In Table 5, the summarised results of the sensitivity analysis, based on the primary outcome of EOGBS-associated infant death avoided, are presented. For the majority of the sensitivity analysis (items 1–8) only the results for Analysis 2 are presented because Analysis 1 is dominated by the 'IAP to all' strategy. In the sensitivity analysis in which the change in cost of IAP is investigated (item 9) the results for both Analysis 1 and Analysis 2 are presented.

The results for the analyses are as follows. (i) Changing the cost associated with EOGBS from £5124.90 (based on estimates from Colbourn *et al.*¹⁶) to £1500, £7500 and £10,000 had no significant effect on the ICER. (ii) When the cost associated with the culture test at 35–37 weeks of gestation is increased to £11.50 from £10.63, the strategy of culture loses its place as the most cost-effective strategy in favour of risk factors. (iii) Changing the estimated effect of intravenous antibiotic therapy on EOGBS disease and infant death, given maternal colonisation, from an odds ratio of 0.17–0.028 causes a favourable change in the ICER for the strategy of screening based on culture at 35–37 weeks of gestation, from £633,000 as estimated in the base case, to £441,000 per EOGBS death avoided. Using the Ohlsson and Shah³⁵ odds ratio of 0.17, which had a wider confidence interval than the Smail odds ratio, did not change the base-case result. (iv) A change in the PCR rapid-test 'accuracy' estimate from that based on vaginal swab only to that based on rectal and vaginal swabs combined had no impact. (v) When the reference standard for determining the accuracy of the OIA and PCR rapid tests is changed from enriched culture of the vaginal and rectal swabs combined to enriched culture of the vaginal swabs only, the strategy of screening based on culture at 35–37 weeks of gestation is still the most favourable with an ICER of £633,000 per EOGBS-associated death avoided. (vi) The threshold analysis shows that, given current accuracy in

terms of sensitivity and specificity, and based on the vaginal swab only, if the cost of the PCR rapid test could be reduced to as low as £7.00 (compared with that of £29.95 estimated in this study), PCR would become the most cost-effective strategy. (vii) Making the same changes as the previous item, if the sensitivity and specificity were based on the vaginal and rectal swab combined, the corresponding cost of the PCR test needs to be £10.00 for the PCR rapid test to be the most cost-effective strategy. (viii) If we removed the assumption that all women who deliver before the screening test based on culture at 35–37 weeks of gestation, are treated with IAP, then the strategy of screening based on risk factors has the most favourable ICER of £658,000 per EOGBS-associated death avoided. As a result of this change, the ICER for the strategy of culture test at 35–37 weeks of gestation increases to a much less favourable £890,000 per EOGBS-associated death avoided. (ix) The average cost of antibiotics was estimated to be £14.28 in the current study. For Analysis 1, the threshold analysis shows that the option of providing antibiotic prophylaxis to all remains the most cost-effective option when the cost of antibiotics is raised to £24.00, at which stage the strategy of culture at 35–37 weeks of gestation also becomes a potentially cost-effective strategy with an ICER of £773,000. This remains the case even when the cost of antibiotics is raised to £50. For Analysis 2, the threshold analysis indicates that the strategy of culture at 35–37 weeks of gestation is the preferred strategy regardless of the cost of antibiotics. This strategy remains the only possible cost-effective option even when the cost of antibiotics is raised to £50.

Discussion

The results of the analysis have shown that both PCR and OIA rapid tests, based on vaginal or rectal swabs, in their current form do not offer a cost-effective option for screening women for GBS colonisation during labour.

The results of this economic evaluation have shown that a strategy of 'Routine untargeted IAP to all' is the most cost-effective strategy compared with 'Do nothing' and relative to all other strategies. The ICERs for the full modelling analysis (based on Analysis 1) are approximately £32,000 per EOGBS disease avoided and £427,000 per EOGBS-associated infant death avoided. The latter ICER in terms of QALYs is approximately £15,800 per QALY. Hence, this strategy is likely to be accepted by decision-makers such as NICE on cost-effectiveness grounds alone.

If we assume that a strategy of IAP to all women may not be acceptable to women or their midwives because of concerns which include antibiotic resistance, risk of ana-phylaxis in penicillin-allergic women and the medicalisation of childbirth^{4,14} and therefore remove it from the analysis

to create Analysis 2, the most cost-effective strategy becomes the culture test at 35–37 weeks of gestation. The ICER for culture at 35–37 weeks of gestation was approximately £45,000 per EOGBS disease avoided and £633,000 per EOGBS-associated infant death avoided. The latter translated to £23,444 per QALY. This exceeds the acceptable threshold set by NICE of £20,000 per QALY so it would not be automatically accepted on cost-effectiveness grounds alone and the uncertainty surrounding this estimate would require greater scrutiny.³⁶ If the assumption that the majority of surviving infants experience full health was considered plausible, then the strategy is more likely to be accepted.

These results, for both Analysis 1 and Analysis 2, were shown to hold for the majority of sensitivity analyses. Two exceptions that occurred in Analysis 2 switched the results to show risk factors becoming the most cost-effective strategy. This happened when either the cost of the culture test was increased by a small amount, or if the base-case assumption, that women who gave birth before the culture at 35–37 weeks of gestation received IAP, was removed.

The strength of this analysis is that the majority of effectiveness and cost data used to populate the options in the model are based on the latest empirical data from the current primary study. Furthermore, robust design and execution of our test accuracy study allows us to be confident that the estimates of accuracy are valid and that our findings from the main study,¹¹ of the superiority of PCR over OIA, are valid. Methodological bias was minimised by ensuring that the index tests and reference standard were performed independently and interpreted blind to each other.

In terms of limitations, it is not clear, or possible to determine exactly what constitutes current practice for prevention of EOGBS in infants in the UK.³⁷ The main comparator for the economic evaluation has been 'Do nothing', and the model has been calibrated to the population prevalence of neonatal EOGBS disease and EOGBS infant mortality. These population morbidity and mortality rates are based on current practice, but current practice is likely to be heterogeneous with regard to the application of risk factors, in terms of whether screening is based on one risk factor, or more than one, or any at all.³⁷ In addition, to determine the transmission rate of GBS from colonised mothers to their infants, we collected and cultured swabs from the external ear canal. There is a risk of these results under-predicting transmission rates because not all swabs from this site will be positive on culture despite it being a frequently colonised site.

In the current study we present results in terms of cost per EOGBS-related death avoided that have been converted into cost per QALY terms based on the strong assumption that surviving infants are in full health. This assumption is

Table 4. Analysis 1 and 2—base-case results: costs, effects and ICERs where outcomes are cost per case of infant EOGBS disease avoided and cost per case of EOGBS-associated infant death avoided

Test/treatment combination	Mean cost per woman*	Difference in costs**	Effectiveness (% of infant EOGBS disease avoided)	ICER***	ICER*** compared with 'No Screening and no IAP'****	Effectiveness (% of EOGBS-associated infant death avoided)	ICER****	ICER**** compared with 'No Screening and no IAP'****
No screening and no IAP	1058.53		99.9524			99.9964		
Risk factors	1063.80	5.26	99.9631	50 000		99.9972	660 000	660 000
Risk factors +ve OIA +ve	1065.26	1.46	99.9567	Dominated		99.9968	Dominated	
Risk factors +ve PCR +ve	1068.33	4.53	99.9584	Dominated		99.9969	Dominated	
Culture test at 35–37 weeks	1069.78	5.99	99.9778	42 000	45 000	99.9982	612 000	633 000
Routine IAP to all	1069.93	0.15	99.9877	24 000	32 000	99.9991	330 000	427 000
Rapid test 2 OIA	1075.60	5.81	99.9635	Dominated		99.9973	Dominated	
Risk factors –ve OIA +ve	1077.00	7.22	99.9695	Dominated		99.9977	Dominated	
Risk factors –ve PCR +ve	1087.70	17.92	99.9742	Dominated		99.9981	Dominated	
Rapid test 1 PCR	1089.46	19.68	99.9700	Dominated		99.9978	Dominated	

*Mean cost per woman presented incrementally, from least to most expensive.

**Difference in costs' and 'Absolute risk reduction' are calculated relative to last non-dominated option.

***ICER based on cost per case of infant EOGBS disease avoided.

****ICERs in the final column are not compared with the previous best strategy but to the main comparator of 'No screening and no IAP'.

*****ICER based on cost per case of EOGBS-associated infant death avoided.

Table 5. Analysis 2*—summary of main results and sensitivity analysis: outcome is cost per cases of EOGBS-associated infant death avoided

	Test/treatment combination	Mean cost per woman	Difference in costs	Effectiveness (% of EOGBS-associated infant death avoided)	Absolute risk reduction	ICER**	Approximate cost per QALY***
Base case****	Culture test	1069.93	11.40	99.9982	0.000018	£633,000 [†]	£23,444 [†]
Changing cost associated with EOGBS death							
£1500	Culture test	1069.87	11.47	99.9982	0.000018	£636,000 [†]	£23,556 [†]
£7500	Culture test	1069.98	11.36	99.9982	0.000018	£630,000 [†]	£23,580 [†]
£10,000	Culture test	1068.19	11.31	99.9982	0.000018	£628,000 [†]	£23,259 [†]
Changing the cost associated with the culture test at 35–37 weeks							
Cost of culture test is £11	Culture test	1070.28	11.74	99.9982	0.000018	£652,000 [†]	£24,148 [†] £28,303 [†]
Cost of culture test is £11.50	Risk factors	1063.80	5.26	99.9972	0.000008	£658,000 [†]	£24,370 [†]
	Culture test	1070.74	6.94	99.9982	0.000001	£693,000 ^{††}	£25,667 [†] £30,003 ^{††}
Changing estimated effect of IV antibiotics therapy on EOGBS given maternal colonisation*****							
	Culture test	1069.30	10.76	99.9989	0.000024	£441,000 [†]	£16,333 [†]
Changing the sensitivity and specificity for rapid test PCR based on vaginal swab only to the sensitivity and specificity based on vaginal and rectal swab combined^{†††}							
	Culture test	1069.07	11.40	99.9982	0.000018	£633,000 [†]	£23,444 [†]
Changing the reference standard for determining the accuracy of the OIA and PCR rapid tests from enriched culture of the vaginal and rectal swabs combined to enriched culture of the vaginal swabs only^{††††}							
	Culture test	1069.93	11.40	99.9982	0.000018	£633,000 [†]	£23,444 [†]
	Risk factors –ve PCR+ve	1087.80	17.87	99.9983	0.000000	£80,219,000 ^{††}	£2,971,074 ^{††}
Threshold analysis: the characteristics required from the rapid test PCR for it to become a contender in terms of cost-effectiveness—changing the cost of the PCR test while its sensitivity and specificity remain unchanged (accuracy based on vaginal swab)							
PCR test costs £7	PCR test	1066.51	7.98	99.9978	0.000013	£608,000 [†]	£22,519 [†]
	Culture test	1069.93	3.42	99.9982	0.000005	£700,000 ^{††}	£25,926 ^{††}
PCR test costs £7.50	Culture test	1069.93	11.40	99.9982	0.000018	£633,000	£23,444 [†]
Threshold analysis: the characteristics required from the rapid test PCR for it to become a contender in terms of cost-effectiveness—changing the cost of the PCR test while its Sensitivity and Specificity remain unchanged (accuracy based on combined vaginal and rectal swab)							
PCR test costs £10	PCR test	1070.12	11.59	99.9983	0.000019	£612,000 [†]	£22,667 [†]
PCR test costs £10.50	Culture test	1069.93	11.40	99.9982	0.000018	£633,000 [†]	£23,444 [†]
Removing the assumption that all women who deliver before the screening test based on culture at 35–37 weeks, are treated with IAP							
	Risk factors	1063.80	5.26	99.9972	0.000008	£658,000 [†]	£24,370 [†]
	Culture test	1069.93	6.13	99.9978	0.000005	£890,000 ^{††}	£32,963 ^{††}
	Risk factors –ve PCR+ve	1087.80	17.87	99.9981	0.000003	£5,390,000 ^{††}	£199,630 ^{††}
Changing the cost associated of IAP treatment							
IAP cost £23.50 ^{†††††}	Routine IAP	1078.50	19.97	99.9991	0.000026	£758,000 [†]	£28,074 [†]
IAP Cost £24 ^{†††††}	Culture test	1072.47	13.94	99.9982	0.000018	£773,000 [†]	£28,630 [†]
	Routine IAP	1079.50	7.03	99.9991	0.000008	£844,000 ^{††}	£31,259 ^{††}
IAP cost £50	Culture test	1079	20.73	99.9982	0.000018	£1,151,000 [†]	£42,630 [†]

*Results based on Analysis 2 unless otherwise stated.

**ICER is per EOGBS-associated infant death avoided.

***Approximate cost per QALY is based on discounted QALYs which are premised on current NICE threshold, and on the assumption that a surviving infant is in full health. A life in full health, discounted at the discount rate recommended by NICE of 3.5% is worth approximately 27 discounted QALYs. Therefore the ICER in natural units is divided by 27 discounted QALYs to estimate the cost per QALY.

****For base case, cost for EOGBS death = £5124.90; estimated effect of intravenous antibiotic therapy on EOGBS, given maternal colonisation = 0.17 (odds ratio based on Smail estimate¹²); sensitivity and specificity used for rapid test PCR based on vaginal swab only = 0.584 and 0.923, respectively.

*****Using the Colbourn estimate.¹⁶

[†]ICER presented compared with the strategy of 'Do nothing'.

^{††}ICER presented incrementally compared with value presented directly above it.

^{†††}Combined swabs: sensitivity = 0.84; specificity = 0.87. Note that the reference standard used to calculate accuracy of the rapid tests is still based on the enriched culture of the vaginal and rectal swabs combined.

^{††††}The sensitivity and specificity figures are presented in Table 2.

^{†††††}Results based on Analysis 1.

likely to lead to the incremental cost-effectiveness ratio being more favourable than is realistic because the probability of no disability following EOGBS is approximately 61.5%.¹⁶ An alternative is to present the results based on the utility values that have been estimated by others.¹⁶ However, there are no robust available data on the quality of life that results from EOGBS disease, and the extent of severity of disability on infants is not known. Colbourn *et al.*¹⁶ present their results in terms of cost per QALY by using proxy estimates of the lifetime impact of meningitis and cerebral palsy caused by EOGBS. However, these estimates do not seem to incorporate utility estimates based on other more likely presentations of EOGBS such as sepsis and pneumonia which together account for 89% of all EOGBS presentations.² Strong assumptions were also applied to their estimates of utilities of different disability groups defined as mild, moderate and severe. By presenting QALYs derived on the explicit assumption of full health we acknowledge that the resulting ICER will appear more favourable than it should but the direction of the bias is explicit and clear.

A key limitation in the analysis occurs in Analysis 1, which shows that providing routine untargeted IAP to all is the most cost-effective option. The full cost associated with such a strategy is likely to have been underestimated primarily because the model has not included any costs associated with potential resistance to antibiotics or adverse effects in this population as well as costs linked to the risk of anaphylaxis in penicillin-allergic women, all of which could lead to complications for the woman or baby in the future. Furthermore, the additional demand and its impact on costs to hospitals, delivery units and neonatal intensive care were not possible to estimate and have not been incorporated into Analysis 1. Adding to this is the likelihood that such a strategy would not be acceptable to the majority of women who are anxious to resist the further medicalisation of childbirth.^{4,14} However, these limitations are reduced in Analysis 2, which provides a valuable assessment and new evidence to policy-makers. This model-based evaluation was restricted to the perspective of the NHS for pragmatic reasons and the main outcomes were presented in terms of cost per case of EOGBS disease avoided and cost per case of EOGBS death avoided to avoid un-validated assumptions about additional costs and lifetime costs. The only primary data being collected in the study were with respect to test accuracy and primary health-service use. Neonatal intensive care costs as well as wider societal costs or impact of the disease on long-term outcomes and the possibility of caring for an individual affected by EOGBS disease were not included because of limited available data. Such cost-estimations would require new primary data on outcomes associated with EOGBS disease. Such data collection was beyond the remit and ethics approval available to the study.

The results show that the strategy of routine untargeted antibiotics to all is the most cost-effective strategy overall. When this is removed from the analysis on the grounds that it is likely to be unacceptable to women, screening based on culture at 35–37 weeks of gestation, with antibiotics given to all those women who deliver before 35 weeks becomes the most cost-effective option.

The results reported by the current study are broadly similar to those reported by Colbourn *et al.*¹⁶ The authors found vaccination was the most cost-effective option, a strategy not considered in the current analysis because there is currently no available vaccine to prevent EOGBS disease. In the absence of vaccination, their study concluded that treatment with antibiotics for high-risk groups and for women who delivered preterm was cost-effective, whereas screening based on culture at 35–37 weeks of gestation was found to be cost-effective for low-risk women.

Colbourn *et al.*¹⁶ used a different estimated effect of intravenous antibiotics therapy on EOGBS disease and death, given maternal colonisation, compared with the current study. Their estimate was much lower at 0.028 (95% CI 0.0015–0.12) than the one reported in the Smail study.¹² Their justification for their use of the alternative estimate is based on opposing schools of thought regarding the use of a fixed effects estimator used in meta-analysis. Colbourn *et al.*¹⁶ (p.45) argue that the Smail estimate is based on the Peto 'one-step' method, which is a fixed effect estimator that they assert produces '...seriously biased estimates when the true treatment effects are large'.^{38,39} Our sensitivity analysis showed that when the alternative estimate used by Colbourn *et al.*¹⁶ was used there was a significant impact on the results, which made the relative ICERs, when compared with 'Do nothing', even more favourable.

In contrast to the current study, El Helali *et al.*⁴⁰ found that the PCR rapid test was more accurate than culture-based screening. The sensitivity they used for culture-based screening was much lower than the estimate used in the current study. Their estimate was based on their own single study whereas the estimate used in the current study is based on a meta analysis.¹⁶

The results show that, based on current evidence, neither of the rapid tests, as evaluated in the current study, should be used in practice because it is clearly not a cost-effective method of screening women for GBS colonisation. It is acknowledged that the time needed for IAP to be effective following a rapid test result was not included in the base-case analysis. If it was, this would have disadvantaged the rapid tests even more.

There is economic evidence to support the serious consideration of the strategy of providing routine untargeted antibiotics prophylactically to women but this is counterbalanced by clinical and other arguments of acceptability, adverse effects and risk of anaphylaxis. There is also

evidence in support of the strategy of testing at 35–37 weeks of gestation based on culture of vaginal and rectal swabs, with antibiotics provided to women who deliver before 35 weeks.

There is a clear need to develop a simple point-of-care test that has a high level of accuracy against the reference standard of culture. Based on their current accuracy performance, the rapid tests, as evaluated in this study, need to be both cheaper and more accurate.

There is also a clear need for studies to explore the quality of life of infants who have experienced EOGBS disease and survived. Value for money of antenatal screening and testing programmes crucially depends on the values attributed to the adverse outcomes averted by testing and these should be the subject of further research and explicit public debate.

Disclosure of interests

All authors declare that the answer to the questions on your competing interest form are all No and therefore they have nothing to declare.

Contribution to authorship

KSK, JG, JD, SB and TER designed the study and were all co-applicants on the funding application. TER and SB designed the economic evaluation. KSK, JG and JD provided clinical advice and data throughout. PM co-ordinated the time and motion study for the rapid testing with the assistance of BK and TER. BK collected cost and resource-use data, constructed the model and carried out the analysis under the supervision of TER. TER drafted the economic section of the initial report. TER and BK co-wrote the first draft of the current paper. All authors, external and internal, had full access to all the data (including statistical report and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors commented on the current paper. TER co-ordinated the economic evaluation of the study and is the guarantor.

Details of ethics approval

Research ethics committee (East London and the City Research Ethics Committee and local research ethics committees) and NHS Trusts' research governance approvals were obtained for recruitment in two large obstetric units, Birmingham Women's Hospital and King George Hospital, Ilford.

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Data sharing

Additional data are available in Daniels *et al.*¹¹

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Supporting information

The following supplementary material is available for this article:

Appendix S1. Time and motion study.

Additional supporting information may be found in the online version of this article.

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