

# Preventive strategies for group B streptococcal and other bacterial infections in early infancy: cost effectiveness and value of information analyses

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## ABSTRACT

**Objective** To determine the cost effectiveness of strategies for preventing neonatal infection with group B streptococci and other bacteria in the UK and the value of further information from research.

**Design** Use of a decision model to compare the cost effectiveness of prenatal testing for group B streptococcal infection (by polymerase chain reaction or culture), prepartum antibiotic treatment (intravenous penicillin or oral erythromycin), and vaccination during pregnancy (not yet available) for serious bacterial infection in early infancy across 12 maternal risk groups. Model parameters were estimated using multi-parameter evidence synthesis to incorporate all relevant data inputs.

**Data sources** 32 systematic reviews were conducted: 14 integrated results from published studies, 24 involved analyses of primary datasets, and five included expert opinion.

**Main outcomes measures** Healthcare costs per quality adjusted life year (QALY) gained.

**Results** Current best practice (to treat only high risk women without prior testing for infection) and universal testing by culture or polymerase chain reaction were not cost effective options. Immediate extension of current best practice to treat all women with preterm and high risk term deliveries without testing (11% treated) would result in substantial net benefits. Currently, addition of culture testing for low risk term women, while treating all preterm and high risk term women, would be the most cost effective option (21% treated). If available in the future, vaccination combined with treating all preterm and high risk term women and no testing for low risk women would probably be marginally more cost effective and would limit antibiotic exposure to 11% of women. The value of information is highest (£67m) if vaccination is included as an option.

**Conclusions** Extension of current best practice to treat all women with preterm and high risk term deliveries is readily achievable and would be beneficial. The choice between adding culture testing for low risk women or vaccination for all should be informed by further research. Trials to evaluate vaccine efficacy should be prioritised.

## INTRODUCTION

Screening to prevent early onset, group B streptococcal infection in neonates is established in the United States, with about 30-50% of women receiving

intravenous prophylactic antibiotics during labour.<sup>1,2</sup> Most other Western countries offer culture-based testing for maternal colonisation with group B streptococci or risk-based testing and treatment. However, screening is not currently recommended in the United Kingdom because of lack of evidence of effectiveness.<sup>3,4</sup>

The controversy centres on three factors. Firstly, is the incidence of early onset neonatal infection high enough in the UK for the benefits to outweigh the costs? Secondly, would the benefits of routine testing be worth while over and above existing use of prepartum antibiotics (such as for maternal fever or preterm rupture of the membranes before the onset of labour)?<sup>4,5</sup> Thirdly, would it be better to await the development of a vaccine for group B streptococcal infection in pregnant women?<sup>6,7</sup> This could be available within the next 5-10 years and would be expected to have an impact on both early and late onset infection in early infancy.

We report the first cost effectiveness analysis to consider the impact of testing for maternal group B streptococcal colonisation, prepartum antibiotic treatment, and vaccination on all types of early onset serious bacterial infection.

## METHODS

### Population, interventions, and outcomes

We constructed a decision model to quantify the effects of different prenatal testing, treatment, and vaccination strategies on serious bacterial infection in early infancy. The pathway of events is shown in figure 1. We separately analysed the intervention strategies for each of 12 maternal risk groups, representing testing and treatment options faced by clinicians assessing a woman presenting in suspected labour (fig 1). The interventions considered were doing nothing; testing vaginal and rectal swabs by culture at 35-37 weeks' pregnancy and treating women with at least one positive result with either oral erythromycin or intravenous penicillin; testing swabs by polymerase chain reaction (PCR) at presentation in labour and treating those with a positive result with oral erythromycin or intravenous penicillin; oral or intravenous treatment without testing; and vaccination at 28 weeks, either given alone or in addition to each of the six other active interventions.

Outcomes were measured in quality adjusted life years (QALYs) gained for births at or after 24 weeks of gestation for the lifetime of the child.

## FAST TRACK

This paper was fast tracked for swift publication

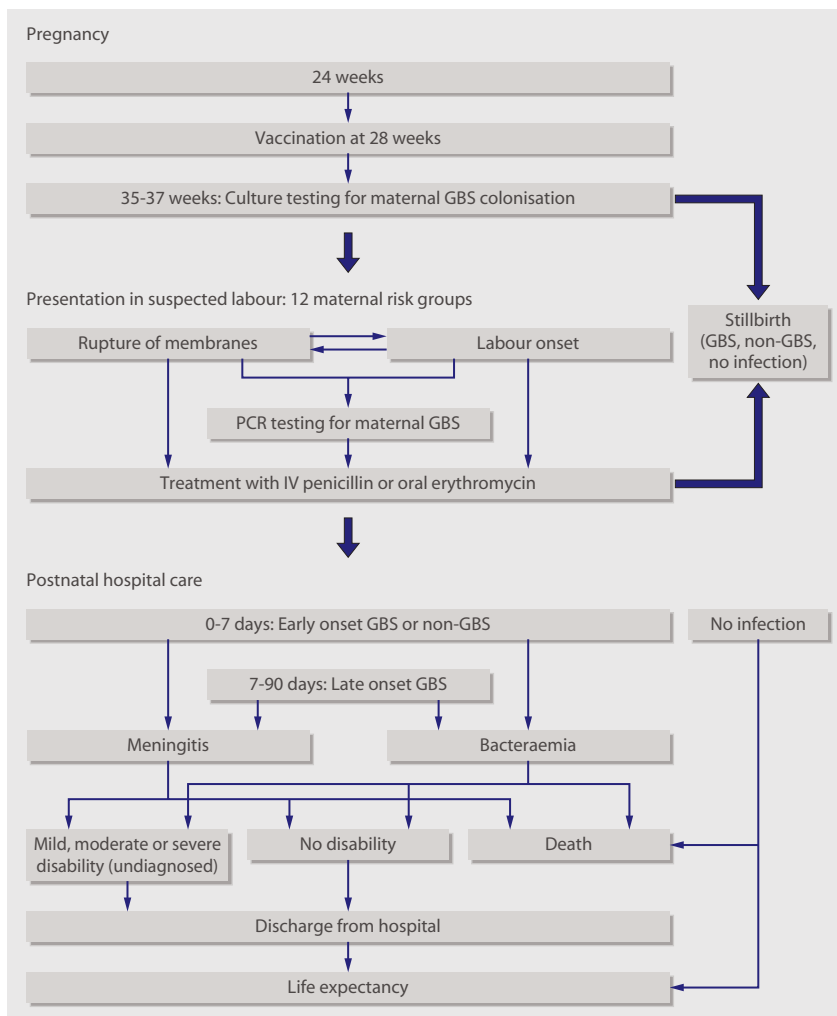
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### Data sources and evidence synthesis

We conducted systematic reviews to answer 32 questions to inform model parameters. We used published studies to answer 14 questions, primary datasets for 24 questions, and expert opinion for five questions. One question (vaccine efficacy) relied solely on expert opinion. Details of each review and data sources are given in the full report.<sup>8</sup>

### Cost effectiveness analysis, decision uncertainty, and value of information analyses

The perspective of the cost effectiveness analysis was the NHS. We calculated the expected costs and QALYs (relative to doing nothing) for each active intervention within each risk group using a threshold of £25 000 per QALY gained.<sup>9</sup>



**Fig 1** | Flow diagram showing sequence of events included in the cost effectiveness model. The 12 maternal risk groups are divided into preterm and term deliveries. Preterm deliveries: 1, planned caesarean section; 2, previous baby with group B streptococcal disease; 3, positive urine or vaginal swab for group B streptococci in current pregnancy; 4, fever  $\geq 38.0^{\circ}\text{C}$  during labour; 5, membrane rupture  $\geq 2$  hours before labour starts; 6, membrane rupture  $< 2$  hours before labour starts. Term deliveries: groups 7 to 10, equivalent to preterm groups 1 to 4; 11, membrane rupture for  $\geq 18$  hours; 12, no risk factors. The risk groups are exclusive and are in hierarchical order. (GBS=group B streptococcal infection, IV=intravenous, PCR=polymerase chain reaction.)

Although antibiotic treatment for all women was the most cost effective option, we judged that universal treatment would be unacceptable because of concerns about antibiotic resistance and the medicalisation of labour. We therefore stipulated that women delivering at term with no risk factors (group 12) could not be treated without a positive test result. We also applied this criterion to term deliveries with prolonged rupture of membranes (group 11) as these two groups are indistinguishable at presentation in suspected labour.

We conducted analyses for each of the 12 risk groups and then for all possible combinations of interventions that had more than a 1% probability of being cost effective in each risk group. We made an exception to the 1% rule to include three intervention strategies relevant to UK healthcare policy for comparison—the recommendations of the Royal College of Obstetricians and Gynaecologists, the college’s recommendations plus oral treatment for preterm ruptured membranes before onset of labour (risk group 5)<sup>10</sup> (which we termed “current best practice”), and the experimental intervention arm of a proposed cluster randomised trial of 540 000 UK women for the Health Technology Assessment (HTA) Programme expected to cost about £12m (Brocklehurst et al, Antenatal screening for group B streptococcus colonisation—protocol development, available at [www.hta.nhsweb.nhs.uk/](http://www.hta.nhsweb.nhs.uk/)).

## RESULTS

### Model parameters

The prevalence of maternal colonisation was twice as high in preterm deliveries as in term deliveries. The overall incidence of early onset neonatal group B streptococcal infection was 0.48/1000 live births but was highest risk in preterm deliveries by women with a previous positive vaginal swab or urine culture for group B streptococci (risk group 3), fever (group 4), or preterm rupture of the membranes before onset of labour (group 5) (see full report<sup>8</sup>). Among term deliveries, the corresponding risk groups (9, 10, and 11) also had the highest risk. Culture testing at 35-37 weeks’ pregnancy had lower sensitivity and specificity (75.8% (95% confidence interval 47.2% to 91.5%) and 94.7% (88.5% to 98.5%)) than PCR testing (89.2% (49.1% to 98.7%) and 95.8% (86.7% to 99.7%)) but was cheaper (£11.99 per woman *v* £19.03 per woman). See [bmj.com](http://bmj.com).

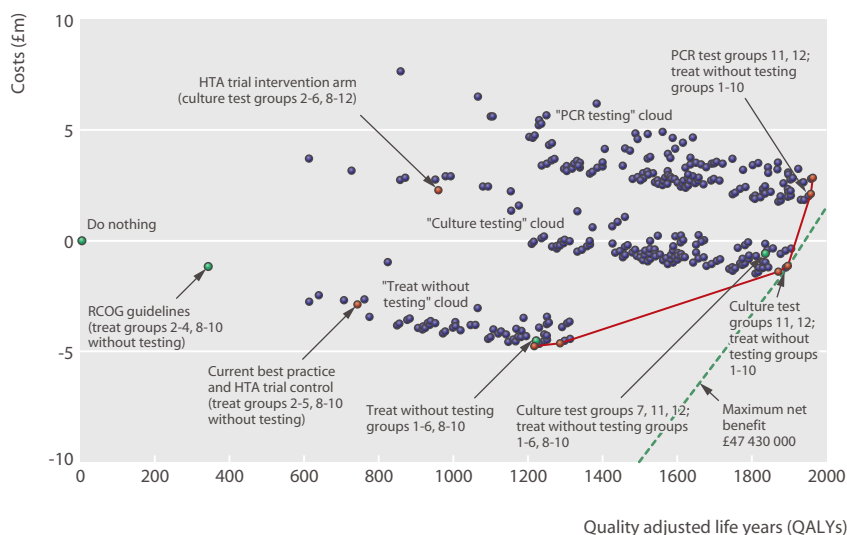
### Cost effectiveness results

Testing for maternal colonisation with group B streptococci was not cost effective for the 20% of women in risk groups 1 to 10. In these groups, maternal testing, whether by culture or PCR, had a probability of  $\leq 1\%$  of being cost effective. Because of the insensitivity of culture testing and the predominance of infection with pathogens other than group B streptococci, women delivering preterm infants were always better off being treated without testing. Whether the greater expense of intravenous treatment compared with oral treatment is outweighed by its greater effectiveness is

uncertain, however. The economic importance of this uncertainty is reflected in the high expected value of information for risk groups 1, 5, and 6. Among term deliveries, the value of information was highest for groups 11 and 12. For the 71% of women with no risk factors, culture testing was most likely to be cost effective, but PCR testing and doing nothing could not be ruled out as potentially cost effective strategies. (See table 3 on [bmj.com](http://bmj.com) for details.)

Figure 2 shows the expected costs and QALYs for each strategy compared with doing nothing. Points to the bottom and right are less costly, provide more QALYs, and have a higher net benefit. The dotted net benefit isoline represents the maximum available net benefit. Separate “clouds” of strategies can be distinguished for treating without testing (lowest cloud), culture testing, and PCR testing (most expensive of the three). Within each cloud, QALYs are gained (moving to the right) by strategies that maximise the proportion of women treated without testing.

The strategy with the maximum net benefit involves culture testing for the low risk, term women (groups 11 and 12). On average, this is the most cost effective option, but several other strategies, with minor changes in treatment for specific risk groups, yield similar net benefit. Replacement of culture testing with PCR testing is only marginally less cost effective because PCR was more sensitive but also more expensive than culture. Current best practice, the recommendations of the Royal College of Obstetricians and Gynaecologists, and the experimental intervention arm of the proposed HTA trial generate substantially less net benefit and are clearly not cost effective. (See table 4 on [bmj.com](http://bmj.com) for details.)



**Fig 2 | Cost effectiveness of strategies (excluding vaccination).** The dotted line denotes maximum net benefit. The red lines denote the cost effectiveness frontier. (HTA=Health Technology Assessment, PCR=polymerase chain reaction, RCOG=Royal College of Obstetricians and Gynaecologists.)

### Minimisation of antibiotic use

Two limitations of our analyses are the exclusion of adverse effects of antibiotics and organisational costs to implement (or reverse) a new intervention. To address these limitations, we propose a series of policy options (see [bmj.com](http://bmj.com)). If policy makers were to limit options to those based on treating only high risk groups without testing or the experimental intervention arm of the proposed HTA trial, pending further research on culture or PCR testing, the probability of being cost effective would be 0.92 for treating all preterm and high risk term women, 0.03 for current best practice, 0.00 for the royal college's recommendations, and 0.05 for the proposed trial intervention.

### Value of information analyses

Assuming that vaccination is not available, the expected value of perfect information for the UK for choosing between all the strategies is £28.9m. Most of the value of information is driven by uncertainty about the choice between intravenous and oral antibiotic treatment for certain preterm groups.

Cost effectiveness analyses show that the gain in net benefit from vaccination, when added to the best non-vaccination strategy is small (£2.1m/year in the UK) and uncertain. Strategies involving testing for low risk women in addition to vaccination prevent more cases of infection but, because of the added cost of testing, produce less net benefit. Vaccination is therefore more cost effective without testing.

If vaccination is included as an option the expected value of information is more than doubled (£67.3m), reflecting the potential but uncertain increased net benefit and increased options. These estimates are moderately large and, although they provide only an upper bound on the value of a new study, clearly exceed the cost of most proposed research in this area.

### DISCUSSION

Our results show that current best practice in the UK is clearly not cost effective. All cost effective options involve treating all preterm and high risk term groups without testing. Testing high risk women for group B streptococcal colonisation would not be cost effective, as even those with negative results would be better off treated to reduce the risk of early onset infection caused by pathogens other than group B streptococcus. Culture testing of low risk term women, combined with treatment without testing for the rest, would be the most cost effective strategy.

Moderate investment in research could be worth while provided studies address the uncertainties highlighted by our analyses. Vaccination plus treatment of all preterm and high risk term women offers a more cost effective strategy with less antibiotic exposure than one involving culture testing of low risk women, but the difference in net benefit is uncertain and based on expert opinion on vaccine efficacy.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Prenatal screening for maternal group B streptococcal infection results in antibiotic treatment for 30-50% of women giving birth in the US

Such screening is not recommended in the UK because evidence is lacking about its effectiveness

**WHAT THIS STUDY ADDS**

Current best practice is not cost effective, and immediate extension of routine antibiotic treatment practice to all preterm and high risk term deliveries would be beneficial and could be readily implemented

Thereafter, it is uncertain whether the optimal choice would be culture based testing for low risk women, or vaccination plus treatment of all preterm and high risk term deliveries and no testing for low risk women

Further research could be cost effective: trials to evaluate vaccine efficacy should be a priority, and trials to evaluate testing versus no intervention in low risk women could be worth while. However, the proposed £12m HTA trial of screening versus current best practice would randomise women to intervention and control groups that are not cost effective

**Strengths and limitations of study**

The strengths of our study include analysis of 12 maternal risk groups to reflect the decision options faced by clinicians and inclusion of all available data that directly and indirectly informed parameters. One limitation is the restriction of outcomes to the current pregnancy.<sup>11</sup> Another is that we focused on culture-positive bacteraemia or meningitis. Also we did not include adverse effects of intrapartum antibiotic treatment on pathogen selection and antibiotic resistance in the net costs or QALYs. As a result, we underestimated the benefits of strategies that involved treating fewer women. We quantified the trade-off that policy makers would need to make in terms of additional women treated per QALY gained.

**Policy issues**

We suggest that policy makers consider immediate extension of current practice to give antibiotic treatment to all women with preterm and high risk term deliveries. Assuming treatment of all preterm and high risk term women is adopted, the most cost effective option would be to add culture testing for low risk women. This option is unlikely to be adopted without further research.

If policy makers judge that vaccination is not an option, the amount worth investing in further information would be £29m,<sup>12</sup> and priorities for further information would be the effectiveness of intravenous versus oral antibiotic treatment in some preterm risk groups on all types of early onset neonatal infection. There would also be value in further information comparing culture testing with PCR testing and no treatment, but only in low risk women delivering at term.

Neither of these questions will be addressed by the proposed HTA trial of culture testing versus current best practice, which also raises ethical concerns about randomising 540 000 women to intervention and control arms that are clearly not clinically or cost effective.

**Conclusions**

Current recommendations for prepartum antibiotic use in the UK should be urgently reappraised with a view to extending treatment to all preterm and high risk term groups. Policy makers should reconsider the value of testing high risk groups for maternal colonisation with group B streptococcal infection, as, given the risk of infection from pathogens other than group B streptococci and the insensitivity of screening, such women may be better off treated regardless of the test result. Research aimed at the realisation of a vaccine for group B streptococcal infection should be a priority.

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