

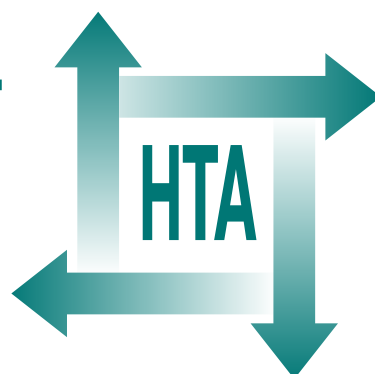
Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness

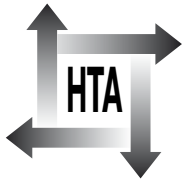
J Daniels, J Gray, H Pattison, T Roberts, E Edwards, P Milner, L Spicer, E King, RK Hills, R Gray, L Buckley, L Magill, N Elliman, B Kaambwa, S Bryan, R Howard, P Thompson and KS Khan



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Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness

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The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 02/38/04. The contractual start date was in October 2004. The draft report began editorial review in October 2007 and was accepted for publication in November 2008. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness

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Objective: To determine the accuracy, acceptability and cost-effectiveness of polymerase chain reaction (PCR) and optical immunoassay (OIA) rapid tests for maternal group B streptococcal (GBS) colonisation at labour.

Design: A test accuracy study was used to determine the accuracy of rapid tests for GBS colonisation of women in labour. Acceptability of testing to participants was evaluated through a questionnaire administered after delivery, and acceptability to staff through focus groups. A decision-analytic model was constructed to assess the cost-effectiveness of various screening strategies.

Setting: Two large obstetric units in the UK.

Participants: Women booked for delivery at the participating units other than those electing for a Caesarean delivery.

Interventions: Vaginal and rectal swabs were obtained at the onset of labour and the results of vaginal and rectal PCR and OIA (index) tests were compared with the reference standard of enriched culture of combined vaginal and rectal swabs.

Main outcome measures: The accuracy of the index tests, the relative accuracies of tests on vaginal and rectal swabs and whether test accuracy varied according to the presence or absence of maternal risk factors.

Results: PCR was significantly more accurate than OIA for the detection of maternal GBS colonisation. Combined vaginal or rectal swab index tests were more sensitive than either test considered individually

[combined swab sensitivity for PCR 84% (95% CI 79–88%); vaginal swab 58% (52–64%); rectal swab 71% (66–76%)]. The highest sensitivity for PCR came at the cost of lower specificity [combined specificity 87% (95% CI 85–89%); vaginal swab 92% (90–94%); rectal swab 92% (90–93%)]. The sensitivity and specificity of rapid tests varied according to the presence or absence of maternal risk factors, but not consistently. PCR results were determinants of neonatal GBS colonisation, but maternal risk factors were not. Overall levels of acceptability for rapid testing amongst participants were high. Vaginal swabs were more acceptable than rectal swabs. South Asian women were least likely to have participated in the study and were less happy with the sampling procedure and with the prospect of rapid testing as part of routine care. Midwives were generally positive towards rapid testing but had concerns that it might lead to overtreatment and unnecessary interference in births. Modelling analysis revealed that the most cost-effective strategy was to provide routine intravenous antibiotic prophylaxis (IAP) to all women without screening. Removing this strategy, which is unlikely to be acceptable to most women and midwives, resulted in screening, based on a culture test at 35–37 weeks' gestation, with the provision of antibiotics to all women who screened positive being most cost-effective, assuming that all women in premature labour would receive IAP. The results were sensitive to very small increases in costs and changes in other

assumptions. Screening using a rapid test was not cost-effective based on its current sensitivity, specificity and cost.

Conclusions: Neither rapid test was sufficiently accurate to recommend it for routine use in clinical

practice. IAP directed by screening with enriched culture at 35–37 weeks' gestation is likely to be the most acceptable cost-effective strategy, although it is premature to suggest the implementation of this strategy at present.



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List of abbreviations

ANOVA	analysis of variance	OR	odds ratio
CEAC	cost-effectiveness acceptability curve	PCR	polymerase chain reaction
CI	confidence interval	POC testing	point-of-care testing
EOGBS disease	early-onset group B streptococcal disease	PROM	prolonged rupture of membranes
FN	false-negative	QALY	quality-adjusted life-year
FP	false-positive	RCOG	Royal College of Obstetrics and Gynaecology
GBS	group B streptococcus (<i>Streptococcus agalactiae</i>)	RCT	randomised controlled trial
HRG	Healthcare Related Group	RR	relative risk
HTA	Health Technology Assessment	SD	standard deviation
IAP	intravenous antibiotic prophylaxis	Sn	sensitivity of a test
ICER	incremental cost-effectiveness ratio	Sp	specificity of a test
IV	intravenous	SPSS	Statistical Package for the Social Sciences
LOGBS disease	late-onset group B streptococcal disease	STAI	State-Trait Anxiety Inventory
MHRA	Medicines and Healthcare Products Regulatory Agency	STATA	statistical package
NICE	National Institute for Health and Clinical Excellence	STARD	Standards for the Reporting of Diagnostic Accuracy Studies
OIA	optical immunoassay	TN	true-negative
		TP	true-positive

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.



Executive summary

Background

Early-onset group B streptococcus (EOGBS) disease is the leading cause of serious neonatal sepsis in developed countries. It is transmitted to neonates during birth from colonised mothers, in whom it is an opportunistic pathogen harboured in the vagina or rectum. Intrapartum antibiotic prophylaxis (IAP) given to the mother reduces the risk of EOGBS disease in the newborn by reduction of maternal transmission and protection of the neonate, providing it is administered sufficiently early before delivery. There is disagreement about the best screening strategies, with the UK currently recommending IAP on the basis of risk factors present at the time of labour. In some countries, screening of women for GBS colonisation is undertaken at 35–37 weeks' gestation with culture of vaginal and/or rectal swabs. This report assesses the accuracy and acceptability of an alternative approach, based on intrapartum rapid testing for maternal GBS colonisation, to determine which women should receive IAP, and models its cost-effectiveness against alternative strategies.

Objectives

This health technology assessment completed three distinct pieces of work:

- to determine the accuracy (sensitivity, specificity, predictive values) of polymerase chain reaction (PCR) and optical immunoassay (OIA) technologies as rapid tests for maternal vaginal and rectal GBS colonisation at the onset of labour using selective enrichment culture as the reference standard
- to determine the acceptability of rapid testing for GBS colonisation among pregnant women of different age and ethnic groups
- to determine the cost and cost-effectiveness of rapid intrapartum testing for maternal GBS colonisation to prevent EOGBS disease, and compare this with other strategies for screening and prevention.

Methods

A primary test accuracy study obtained swabs at the onset of labour from 1400 women from two large maternity units to compare the results of vaginal and rectal PCR and OIA (index tests) with the reference standard of enriched culture of combined vaginal and rectal swabs. The study compared the accuracy of index tests, determined the relative accuracies of tests on vaginal and rectal swabs, evaluated whether test accuracy varied according to the presence or absence of maternal risk factors, and explored the determinants of neonatal colonisation.

Acceptability of testing to participants was evaluated through a structured questionnaire administered as soon as possible after delivery. The characteristics of those who declined to take part in the study when first approached were also analysed. Acceptability of rapid testing to staff was evaluated through two focus groups with midwives who had taken part in the study.

For the economic evaluation resource usage data were collected alongside the test accuracy study to establish the cost of rapid testing. A decision-analytic model was constructed to assess the cost-effectiveness of various screening and prevention strategies, using a perspective of the NHS and an outcome of cost per case of EOGBS disease or death avoided.

Results

Main findings of test accuracy study

PCR was significantly more accurate than OIA for the detection of maternal GBS colonisation, for all combinations of index and reference test. Combined vaginal or rectal swab index tests were more sensitive than either test considered individually [combined swab sensitivity for PCR 84% (95% CI 79–88%); vaginal swab 58% (52–64%); rectal swab 71% (66–76%)]. The highest

sensitivity for PCR came at the cost of lower specificity [combined specificity 87% (95% CI 85–89%); vaginal swab 92% (90–94%); rectal swab 92% (90–93%)]. The sensitivity and specificity of rapid tests varied according to the presence or absence of maternal risk factors but not consistently. PCR results were determinants of neonatal GBS colonisation, but maternal risk factors were not.

Overall levels of acceptability for rapid testing amongst participants were high and there was no evidence that screening had raised anxiety. They did not find the process of swabbing unpleasant, although vaginal swabs were more acceptable than rectal swabs. Compared with white British women, South Asian women were less likely to have participated in the study and were less happy with the sampling procedure and with the prospect of rapid testing as part of routine care; they were also more likely to prefer professional judgement as the basis for treatment. Midwives were generally positive towards rapid testing if practical problems could be overcome but had concerns that it might lead to overtreatment and unnecessary interference in births.

The rapid tests were both relatively expensive compared with the other strategies (PCR test £29.95; OIA test £16.09). Modelling analysis revealed that the most cost-effective strategy was to provide routine IAP to all women without screening. As this was deemed unlikely to be acceptable to the majority of women and midwives, the analysis was repeated with the removal of this strategy. Here, screening based on a culture test at 35–37 weeks' gestation, with the provision of antibiotics to all women who screened positive, was most cost-effective, assuming that all women

in premature labour would receive IAP. The results were sensitive to very small increases in costs and changes in other assumptions. Screening using a rapid test, whether PCR or OIA, and based on rectal or vaginal swabs combined, was not cost-effective, based on its current sensitivity, specificity and cost.

Conclusions

Implications for health care

Although PCR performed better than OIA, neither rapid test evaluated was sufficiently accurate to recommend it for routine use in clinical practice. Rectal swabbing was less acceptable and the technologies need to be further refined for point-of-care use. The most cost-effective approach to reducing EOGBS disease is likely to be the provision of IAP to all women without testing. If this strategy is discarded on grounds of acceptability, IAP directed by screening with enriched culture at 35–37 weeks' gestation, with IAP to all women in premature labour, becomes cost-effective. However, it is premature to suggest the implementation of either strategy at present.

Recommendations for research

The relative effectiveness, feasibility and acceptability to women of screening by enriched culture and provision of routine IAP should be explored. Further refinements of rapid tests would be required to improve accuracy to make point-of-care testing practicable at reduced cost. Any new development would require further evaluation and comparison with existing strategies.

Chapter I

Introduction and background

Group B streptococcus

Group B streptococcus (GBS) is the leading cause of serious neonatal sepsis in developed countries. Infections are classified as being early onset (presenting in the first week of life) or late onset. The majority of cases of early-onset GBS (EOGBS) disease occur within 24 hours of delivery and present as a rapidly progressive septicaemic illness. Late-onset (LOGBS) disease occurs between 7 days and 3 months of age and is more often associated with localised infections (especially meningitis and pneumonia) that are less rapidly progressive than EOGBS disease. Another important distinction between EOGBS and LOGBS disease is that the former is considered to be directly related to intrapartum exposure to GBS, whereas other routes of acquisition account for a significant proportion of LOGBS disease.

In adults, GBS is an occasional cause of serious systemic infection in immunocompromised patients, but it is more commonly seen as an opportunistic pathogen of the female urogenital tract. Intrapartum antibiotic prophylaxis (IAP) given to the mother reduces the risk of EOGBS disease in the newborn by reducing maternal transmission and protecting the neonate, providing it is administered sufficiently early before delivery. IAP is usually administered to those mothers for whom a risk of mother to baby transmission is identified. At present in the UK, decisions concerning the administration of IAP are usually based on the presence of risk factors at the time of labour. In some countries, for example the USA, screening of women for GBS colonisation is undertaken at 35–37 weeks' gestation to enable decisions to be made about IAP. Neither of these approaches is without drawbacks. This report assesses the accuracy and acceptability of an alternative approach based on intrapartum rapid testing for maternal colonisation to decide which women should receive IAP, and models its cost-effectiveness against alternative approaches.

Epidemiology of neonatal GBS disease

Understanding the epidemiology of EOGBS requires consideration of maternal colonisation

with GBS, the risks and timing of vertical transmission, and the pattern of neonatal colonisation and disease.

Maternal GBS colonisation

The gastrointestinal tract is the natural reservoir of GBS in humans and is the likely source of vaginal colonisation. Asymptomatic colonisation of the genital and lower gastrointestinal tracts with GBS has been reported at a rate of 10–30% in pregnant women,¹ although this figure can vary with age, sexual activity, race and the method of laboratory culture for its detection.² A single vaginal or anal tract swab during pregnancy has been shown to have a poorer predictive value for neonatal sepsis than either multiple site swabbing or repeated culture from a single site.³ Boyer *et al.*⁴ noted that, although 35% of their sample of pregnant women were colonised with GBS at some point in pregnancy, only 17% were persistent carriers and some lost or gained GBS strains during the pregnancy. Nine UK studies of untreated women in labour have suggested rates of maternal colonisation of 5–15% based only on vaginal culture^{5–7} and 15–21% if both vaginal and rectal swabs are cultured.^{8–11} The mean colonisation rate for all studies is 13.6% (95% CI 9.6–18.3%).¹²

There is ample evidence to suggest that the lower gastrointestinal tract is the main reservoir and often the primary culture site for new GBS strains and that lower gastrointestinal tract colonisation is more persistent than vaginal colonisation.^{4,13,14} Urinary tract infections due to GBS are also associated with perinatal infection and late spontaneous abortion.¹⁵

Transmission

Neonates with early-onset infection show initial colonisation mainly in the mucous membranes of the respiratory tract, and the major route of vertical transmission at the time of delivery is thought to be through aspiration of vaginal and amniotic fluid. Vertical transmission in utero is also thought to occur as a consequence of prolonged rupture of membranes (PROM) and is regarded as one of the causes of stillbirth.¹⁶ Colonisation of the mother is less predictive for late-onset GBS infection, with prematurity the major risk factor.¹⁷

The association between the rates of maternal colonisation, transmission and infection has been established. A meta-analysis¹² of six studies of the maternal and baby colonisation rates in an untreated general population showed a transmission rate of 36.4% (95% CI 28.1–45.0%). A further meta-analysis in the same report of EOGBS disease in colonised babies of untreated mothers gave an average incidence of 3.0% (95% CI 1.6–4.7%).

These rates, as illustrated in *Figure 1*, project an overall incidence of 1.5 cases per 1000 deliveries, with a potential range of 0.4–3.9 cases per 1000. This is consistent with a reported incidence from a surveillance population of 0.47 (95% CI 0.42–0.52) cases of EOGBS per 1000 live births.¹⁸

Epidemiology of early-onset GBS disease

In countries where use of IAP is widespread the incidence of EOGBS disease has decreased, but GBS remains one of the most important causes of severe early-onset infection in newborn infants in most industrialised countries. In the USA the incidence of neonatal EOGBS disease has fallen from 1.7 per 1000 in the early 1990s to 0.3 per 1000 in 2004. Likewise, in Australasia the incidence fell from 1.43 per 1000 in 1993 to 0.25 per 1000 in 2001. In Denmark between 1992 and 2001 the incidence was 0.73 per 1000, with a reduction noted during the period of study. Enhanced surveillance in the UK and Ireland between 2000 and 2001 showed an incidence of culture-proven neonatal EOGBS disease of 0.48 per 1000 live births. It is highly likely that some cases of serious neonatal sepsis caused by GBS are unrecognised because cultures of blood and cerebrospinal fluid are negative. By taking into account superficial swab culture results from all neonates who underwent a septic screen in the first 72 hours of life, Luck *et al.*¹⁹ concluded that the true incidence of neonatal EOGBS disease in the UK may be as high as 3.6 per 1000 live births, over seven times higher than previously estimated.

In the 1970s, mortality rates from EOGBS disease as high as 50% were reported, but with advances in intrapartum and neonatal care these have

fallen. In 2001, a national UK surveillance study¹⁸ identified 376 cases, of whom 39 (10.4%) died.

Mortality is much higher in preterm babies: Oddie and Embleton²⁰ found that preterm infants comprised 38% of all cases and 83% of the deaths. Information on morbidity amongst survivors is less clear, but significant long-term morbidity, including impaired psychomotor development, has been reported in up to 30% of survivors.²¹

Risk factors for neonatal GBS disease

Various factors at the time of birth have been shown epidemiologically to increase the risk of GBS disease, presenting either as early- or late-onset infection. A recent systematic review¹² estimated that 71% of deliveries had no recognised maternal risk factors for GBS disease.

Prematurity

Colonised premature babies are at a high risk of EOGBS disease as their immune system is immature and they are less likely to have received passive immunity transplacentally. The pooled incidence of EOGBS disease from five UK studies^{22–25} showed that 40% of cases were preterm deliveries, which translates to a 5.5-fold higher risk for preterm babies than for term babies. Birthweight is highly correlated with prematurity and inversely related to EOGBS disease. The surveillance study by Heath *et al.*¹⁸ indicated an incidence of 4.0 early-onset cases per 1000 deliveries in babies under 1500 g compared with 0.49 cases per 1000 overall.

Prolonged rupture of membranes

Premature or prolonged rupture of membranes would be expected to lead to an increased likelihood of ascending infection and baby colonisation in utero, although there is debate as to whether GBS induces PROM, for example by producing proteases. Rupture of the membranes more than 18 hours before delivery was significantly associated with EOGBS disease with an odds ratio (OR) of 25.8 (95% CI 10.2–64.8) compared with non-infected infants.²⁰

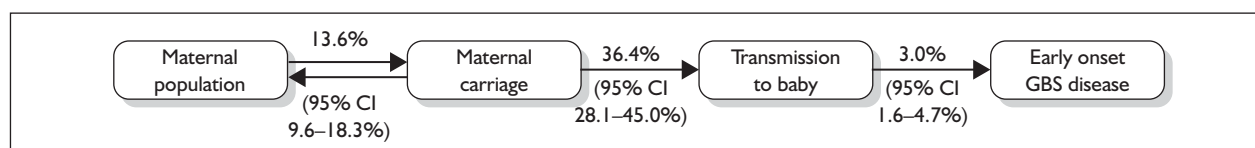


FIGURE 1 Model of colonisation and transmission of group B streptococcus (GBS) and early-onset GBS disease.

Maternal fever

Pyrexia is a symptom of chorioamnionitis or endometritis and may be associated with more intense maternal and baby colonisation.²⁶ Intrapartum fever is also highly associated with EOGBS disease (OR 10.0, 95% CI 2.4–40.8).²⁰

Previous GBS baby

Given the low incidence of GBS it is difficult to reliably estimate the increased risk of EOGBS disease in a subsequent pregnancy.

GBS detected in pregnancy

Data from four studies of women with GBS bacteriuria in labour produced a pooled prevalence of maternal GBS colonisation in labour of 78% (95% CI 63–90%).^{27–30} The association with GBS colonisation in labour, given a previous positive urine or vaginal swab, depends on the time interval between the two tests. Therefore, the above prevalence is likely to be an overestimate as screening for GBS was undertaken concurrently in urine and vaginal samples.

Detection of maternal GBS colonisation

There are several methods of detection of GBS from rectovaginal swabs, with bacterial culture regarded as the definitive approach to detection and discrimination.

Bacteriological culture

GBS grows on blood agar plates, forming characteristic glossy white colonies surrounded by areas of β -haemolysis after 24–48 hours. The use of a selective enrichment broth before plating is widely recommended to optimise the recovery of GBS from genital and anorectal samples, increasing the recovery rate by over 50%.³¹ Lim broth, comprising a Todd–Hewitt base with nalidixic acid and colistin to suppress gram-negative bacteria, is the most widely used enrichment media before plating on to blood agar, although the necessity of selective enrichment has been questioned.³² Obtaining swab specimens from both vaginal and rectal sites increases the incidence of maternal GBS colonisation by 40% over vaginal swabs only.^{33,34}

Rapid tests with timely screening potential

Several non-culture-based tests are available that could be developed into rapid point-of-

care diagnostic tools for intrapartum screening. This would allow optimal targeting of IAP to women carrying GBS during labour. As well as being accurate, the ideal test would need to be rapid enough to allow adequate time for IAP to be effective, and would require minimal preparatory steps and be easily interpretable to enable routine use on busy delivery suites. Each of the tests currently available has advantages and disadvantages. Even laboratory-based use of these tests is limited, and there has been no proper evaluation of any of these tests in the point-of-care setting.

Polymerase chain reaction

Polymerase chain reaction (PCR) involves the logarithmic amplification of specific areas of the bacterial chromosome using an iterative process of hybridisation of replication primers, amplification from these primers of the target DNA and separation of the nascent DNA so that the process can be repeated. Real-time detection of the amplified DNA is by incorporation of a fluorescent marker, which is quantitatively measured within the PCR thermocycler (the Cepheid SmartCycler®, www.cephheid.com). The net effect of this is to reduce the results turnaround time from 12–24 hours to less than 2 hours. One of the main disadvantages of current PCR technology is the lengthy preparative steps required to extract DNA before the thermocycling process can be undertaken.

Optical immunoassay

In the optical immunoassay (OIA) an antibody specific to a GBS surface carbohydrate is coated on a sample well. In the presence of GBS carbohydrate the optical substrate of the test well reflects differently and can be detected visually using a luminometer (Inverness Medical BioStarOIA®, www.invernessmedicalpd.com). Again there is a preparative step, to extract the carbohydrate antigen from GBS.

DNA hybridisation

Nucleic acid hybridisation tests are based on the ability of complementary nucleic acid strands to specifically align and associate to form stable double-stranded complexes. Commercially available kits use a single-stranded DNA probe with a chemiluminescent label that is complementary to GBS ribosomal RNA. A preparatory step releases the RNA from the organism, to which the labelled DNA probe combines to form a stable DNA:RNA hybrid. A specific reagent enables the differentiation of hybridised probe

from unhybridised probe and measurement in a luminometer, with a positive result being one that is greater than a predefined threshold (Gen-Probe AccuProbe®, www.gen-probe.com).

Enzyme-linked immunosorbent assay

Similar to the OIA, the enzyme-linked immunosorbent assay (ELISA) employs antibodies to GBS surface carbohydrate, both coated on a sample well and in soluble form linked to an enzyme. The GBS binds first to the sample well and then the soluble form of the antibody binds to the GBS. The enzyme then produces a reaction in a coloured substrate, which can be detected by eye or quantitated in a luminometer.

Latex agglutination

The simplest of all of the tests relies on antibodies bound to latex particles. If GBS is present, the antibodies bind to its surface and the attached latex agglutinates into visible clumps.

Accuracy of rapid tests for GBS

To determine the accuracy and rapidity of various intrapartum maternal GBS colonisation tests we conducted a systematic review of the literature.³⁵ A systematic search for test accuracy studies, identified without language restriction, was performed on the MEDLINE and Cochrane databases, bibliographies of known primary and review articles, and through contact with authors, experts and manufacturers. From a total of 1296 citations, 23 relevant papers of 29 test accuracy studies assessing a total of six tests were identified. The majority of excluded papers assessed tests antenatally.

The quality of the included studies was assessed using a standard checklist of indicators of methodological bias. Studies were considered to

be of high quality if they reported a prospective design, consecutive patient enrolment, an adequate test description, blinding of the test results and use of selective medium for incubation of specimen for gold standard culture. Unfortunately, as shown in *Figure 2*, the quality of the studies and reporting thereof was poor, and only three were large enough (sample size > 1000) to give reasonable precision.

The prevalence of maternal GBS colonisation in these studies varied from 5% to 32%,^{36,37} yet none explored the variation in the test's performance across a spectrum of population subgroups. Most studies obtained vaginal swabs for tests and gold standards without speculum examination. Only four studies assessed the accuracy of rectal swabs. None of the studies considered the acceptability of testing during labour from the women's or health-care providers' perspectives, nor the costs or cost-effectiveness of the testing strategies.

The review shows that many of the GBS tests, with the exception of real-time PCR and OIA, either took too long to produce a result or were not of sufficient accuracy to be feasible for maternal intrapartum testing. The review focused on studies in which selective media were used for gold standard culture. Exploration of the reasons for heterogeneity in the primary study results was hampered by the small number of studies included in the review. Pooled data produced summary sensitivities and specificities, shown for PCR in *Figure 3* and for OIA in *Figure 4*. PCR had a pooled mean sensitivity of 97% (95% CI 94–98%) and a pooled mean specificity of 97% (95% CI 96–98%). Pooled sensitivity for OIA was 55% (95% CI 48–61%) and pooled specificity was 96% (95% CI 95–97%). Metaregression analysis showed that test accuracy did not vary according to overall quality ($p = 0.58$) or the addition of anorectal swab ($p = 0.064$). Funnel plot analysis did not show any

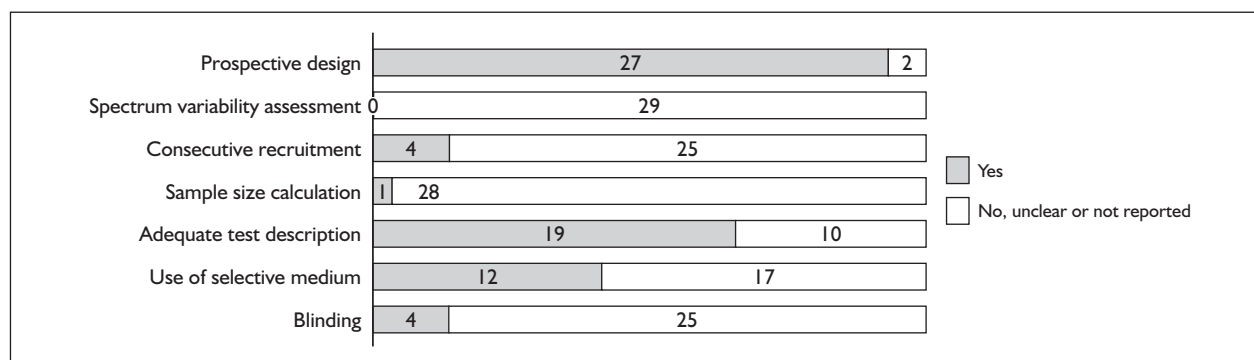


FIGURE 2 Methodological quality of studies included in the systematic review of intrapartum tests for maternal group B streptococcus (GBS) colonisation.

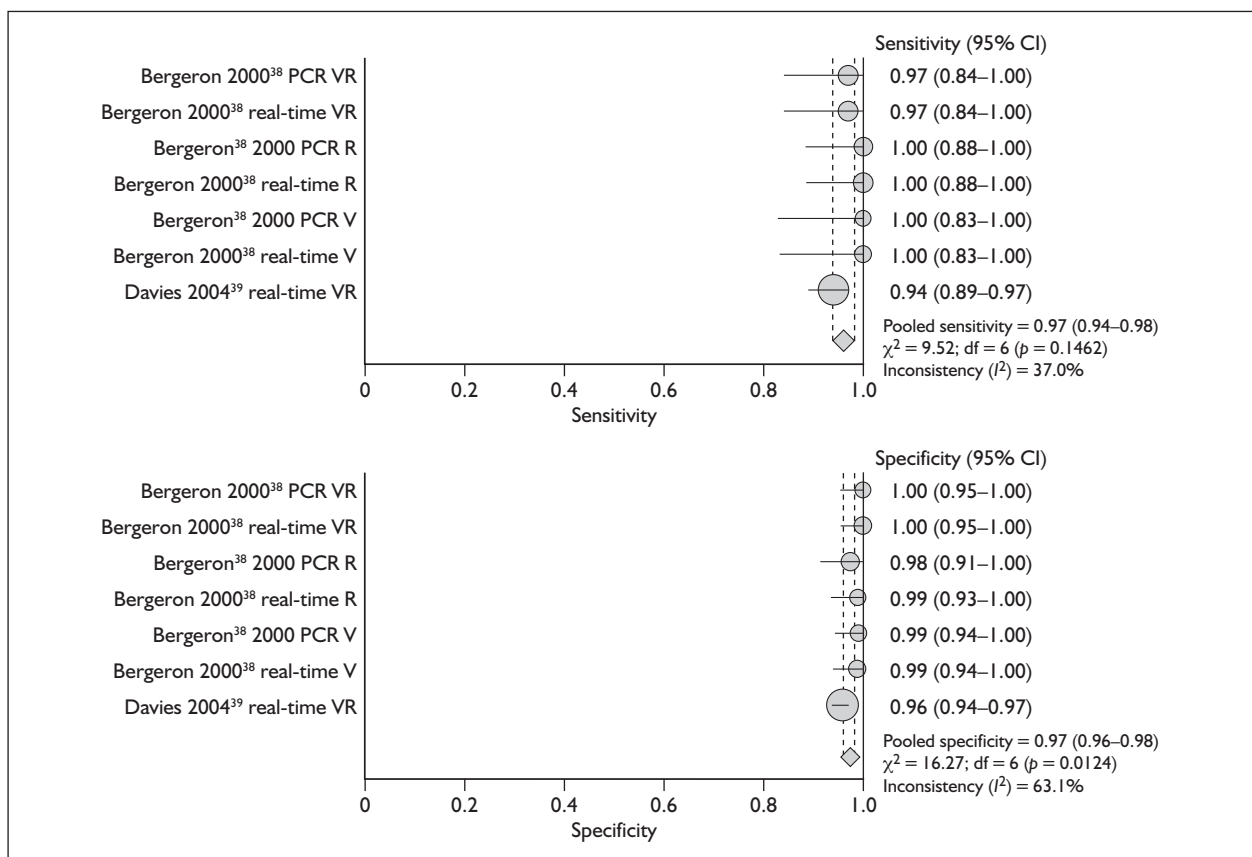


FIGURE 3 Summary of pooled sensitivity and specificity for intrapartum polymerase chain reaction (PCR) testing for maternal group B streptococcus (GBS) colonisation (studies using selective enrichment culture as reference only). PCR, conventional PCR; real-time, real-time PCR; R, rectal sample; V, vaginal sample.

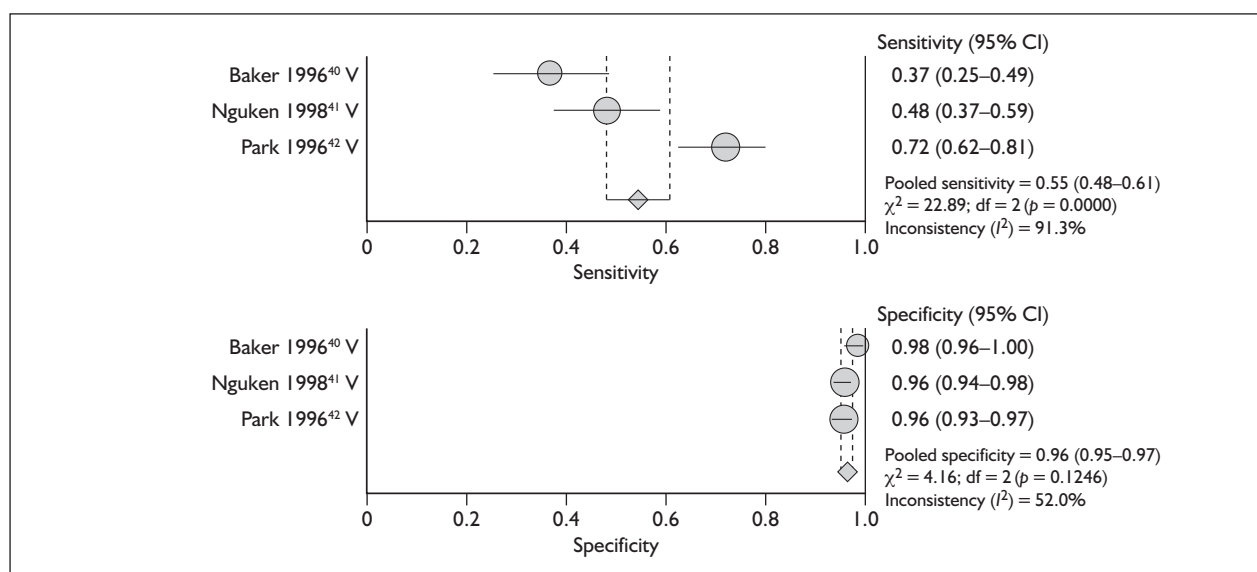


FIGURE 4 Summary of pooled sensitivity and specificity for intrapartum optical immunoassay (OIA) testing for maternal group B streptococcus (GBS) colonisation (studies using selective enrichment culture as reference only). V, vaginal sample.

evidence of asymmetry to indicate the presence of publication or related bias for the largest subgroup of studies.

Although OIA seems less accurate than PCR, it was more rapid and less complex to perform, making it more feasible as a near-patient test. The relative accuracy of the two tests remains unclear because of the poor quality of previous accuracy studies and the absence of any direct comparison against a common standard. This systematic review highlighted a clear need for a well-designed accuracy study comparing PCR and OIA tests, the subject of this Health Technology Assessment (HTA) report.

Intrapartum antibiotic prophylaxis for preventing neonatal GBS

A Cochrane systematic review⁴³ of five randomised trials has shown that intrapartum antibiotic treatment of mothers with GBS colonisation or risk factors in the third trimester or during labour reduces neonatal GBS colonisation by 90% (summary OR 0.1, 95% CI 0.07–0.14) and EOGBS disease by approximately 80% (summary OR 0.17, 95% CI 0.07–0.39). The methods for identifying colonised mothers and affected infants varied considerably between studies. Two studies used rapid testing (latex agglutination)^{44,45} and three studies used standard culture in selective medium to test for maternal GBS.^{46–48} There were also considerable variations between studies in methods of determining neonatal colonisation and disease. The most commonly used methods for detecting neonatal GBS were body surface swabs, for example skin surface and oropharyngeal cavity, umbilicus^{44–48} and urine testing.^{44,45,47} Although it is recommended that IAP commences at least 4 hours before delivery there is little evidence as to the optimum duration of treatment.⁴⁹

Another Cochrane review^{50,51} showed that there is insufficient evidence from randomised controlled trials (RCTs) to recommend routine intramuscular penicillin prophylaxis for the neonate to prevent early-onset disease. Although this finding is contradictory to those of earlier non-randomised studies,^{52–55} it is highly likely that postnatal antibiotics are insufficient to eliminate infection that is already established at birth. Moreover, this approach may increase neonatal mortality from antibiotic-resistant gram-negative bacteria,^{26,56} although the relative contributions to any increase

in mortality of intrapartum and postnatal antibiotic use are debatable.^{57,58}

Screening and prevention of GBS

A screening programme is directed to a population that may be at risk of a disease or its complications and offers one or more tests to identify those who need further investigation or treatment. Screening targets apparently healthy people and provides them and health professionals with information on which to make informed choices about their health. It can potentially reduce morbidity and improve quality of life through early diagnosis, but there are disadvantages and any screening programme should be systematically evaluated before implementation as a public health policy. Primary screening aims to identify those at risk and reduce those risks; secondary screening should detect cases early enough to effect worthwhile treatment; and tertiary screening seeks to minimise complications of the disease.

There are several screening and prevention strategies proposed to prevent EOGBS disease.

Risk factor-based screening

Risk factor-directed screening is based on the assessment of women at labour for the presence of one or more of the risk factors described in the previous section on risk factors for neonatal GBS disease. IAP may then be offered to those with risk factors.

This approach was introduced in the UK in 2001 when the GBS Working Group of the Public Health Laboratory Service produced interim guidelines.^{59,60} These recommended IAP specifically for women who had had a previous GBS-infected baby or when GBS was found incidentally in the vagina or urine during the current pregnancy. It was also recommended that IAP should be considered for preterm births, when the mother has intrapartum fever and/or when there is PROM in labour. For mothers requiring broad-spectrum antibiotic therapy for chorioamnionitis it was recommended that the chosen regimen should include activity against GBS.

This strategy was endorsed by the Green-top Guideline of the Royal College of Obstetrics and Gynaecology (RCOG) in 2003.⁶¹ The guidelines were revised slightly in 2004 when the Health

Protection Agency advised that IAP should be considered only when GBS is detected incidentally in pregnancy.⁶²

Bacteriological screening at 35–37 weeks' gestation

This approach involves the culturing of vaginal and rectal swabs from all women between 35 and 37 weeks of gestation and offering IAP to those in whom GBS is detected. Inevitably, results will not be available in time for all women screened this way, either because of prematurity or delivery before the results are available. Women with missing culture results can be either treated on the basis of risk factors or automatically offered IAP. However, culture-based approaches rely on colonisation at the time of swab collection being predictive of colonisation status at the onset of labour.

In the USA interim guidelines produced in 1996 suggested that either a risk factor- or a culture-based approach should be adopted but that IAP should be offered to all those considered at risk.^{56,63} The risk factors considered as definite indicators for IAP were preterm delivery, PROM (> 18 hours) or intrapartum fever. Under both strategies women with GBS bacteriuria during their current pregnancy, or who previously gave birth to an infant with EOGBS disease, were candidates for IAP.

These guidelines were revised in 2002 to recommend universal screening by culture of 35- to 37-week swabs. Women in labour for whom the culture status was not known would be screened on the basis of risk factors. Further refinements included advice for penicillin-hypersensitive women and an algorithm for threatened preterm delivery, otherwise recommendations from 1996 were retained.

A meta-analysis³¹ of four studies, involving nearly 4000 women, assessing the accuracy of culture at 35–37 weeks, with colonisation status at delivery as the reference standard, has recently been performed. The mean sensitivity was 76% (95% CI 47–92%) and mean specificity 95% (95% CI 89–99%). This sensitivity estimate is 21% lower than that for PCR in the review by Honest *et al.*,³⁵ suggesting that PCR could be a promising alternative to culture. This would require confirmation through an RCT.

Vaccination

Vaccination of pregnant women offers the opportunity for primary prevention of GBS disease by two mechanisms. First, a vaccine that induces mucosal immunity would decrease maternal colonisation and consequently the risk of transmission to the baby. Potentially more important would be the transplacental transmission of protective antibodies to the baby. Babies with low concentrations of antibodies to GBS proteins have an OR of 0.002 of developing EOGBS disease compared with those with greater levels.⁶⁴ Protective maternal antibodies are believed to persist in the baby for about 3 months after birth,⁶⁵ affording additional passive protection against late-onset disease.

The search for a suitable candidate molecule for vaccination has been ongoing for two decades, but a vaccine has yet to be licensed for use and evaluated for effectiveness in reducing neonatal GBS disease. Initial developments involved carbohydrate-based vaccines, and immunogenic efficacy has been demonstrated in women.⁶⁶ The major disadvantage to this approach is that there are five major, and several minor, serotypes of GBS, each with a different outer carbohydrate, and so any vaccine would have to be multivalent and appropriate to the serotype prevalence within the population. Focus therefore shifted to a ubiquitous protein that is present on the outer surface of all GBS serotypes.⁶⁷ Protein-based antigens are inherently more immunogenic than carbohydrates, are less likely to cross-react with human tissues and can more readily be manipulated by molecular techniques. Phase 1 trials have been conducted for one protein candidate.⁶⁸

With all candidate vaccines, to definitively demonstrate effectiveness would ultimately require a placebo-controlled trial with a reduction in the incidence of GBS disease. Given the low incidence of disease, this would require an unfeasible number of participants. Surrogate outcomes, such as neonatal antibody titre, would need to be accepted by licensing authorities before a vaccine could be approved. For the purpose of this study, and the modelling of cost-effectiveness, the data and assumptions used in the cost-effectiveness analysis of Colbourn *et al.*⁶⁹ are used.

The evidence base for screening strategies

In the USA the incidence of EOGBS disease fell from 1.7 per 1000 live births in the early 1990s

to 0.5 per 1000 a decade later and 0.34 per 1000 in 2004.^{70,71} Implementation of the 1996 policy was widespread, with over 90% of women being screened by culture at 35–37 weeks' gestation.⁶³ Both risk factor- and culture-based strategies can lead to a reduction in the incidence of EOGBS disease, although, because of the large sample size required, the strategies have not been directly compared in a randomised trial.⁶³ A direct non-randomised comparison of the strategies,⁷² incorporating population-based surveillance for EOGBS disease into a sample survey of a population of over 600,000 live births, found that the culture-based screening approach was >50% more effective than the risk-based approach at preventing perinatal GBS disease. Amongst the cohort who underwent screening by culture, 18% of all deliveries were to GBS colonised mothers who did not have risk factors. A greater proportion of GBS colonised women received IAP than those with obstetric risk factors, although overall 24% of women in each cohort received IAP. Had implementation been perfect, 31% of all women screened by culture and 29% screened under the risk factor strategy would have received IAP.

The UK has not adopted a similar culture-based policy, despite pressure to do so, as there is no evidence of its clinical effectiveness and cost-effectiveness in the UK setting. The incidence of EOGBS disease in the UK in the absence of systematic screening or widespread IAP is 0.5 per 1000 births,¹⁸ which is similar to that seen in the USA after universal screening and IAP, despite comparable maternal colonisation rates. It is estimated that, in the UK, assuming that 30% of women receive IAP because of GBS colonisation and that IAP is 80% effective at preventing GBS infection, 714 colonised women would need to receive IAP to prevent one case of GBS disease and over 7000 would need to receive IAP to prevent one neonatal death.⁶¹ Actual efficacy rates may be lower than this estimate. A national swab-based screening programme would require a substantial reorganisation of the provision of antenatal care in the UK.

Neither the risk factor approach nor culture-based screening at 35–37 weeks is ideal. The risk factor-based approach is inherently crude, with only 60% of EOGBS disease cases having risk factors apparent at labour.^{18,20} Screening at 35–37 weeks' gestation may result in those pregnancies at highest risk of GBS disease being missed: in the UK, 7.4% of births occur before 37 weeks, whereas 32–38% of GBS disease occurs in these neonates.^{20,22}

Additionally, antenatal screening and treatment has not been shown to have an effect on all-cause neonatal mortality⁴³ and may carry disadvantages for the mother and baby. These include potentially fatal anaphylaxis,⁷³ medicalisation of labour and the neonatal period, and neonatal infection with antibiotic-resistant bacteria. The risk of neonatal infection has still not been fully elucidated. One US study showed an increase in the incidence of *Escherichia coli* infection in low-weight neonates, comparable to the decline in GBS.⁷⁴ Other studies have not confirmed this finding, and it is also possible that the use of benzylpenicillin as IAP in the UK may exert less selective pressure than the broader-spectrum antibiotics often used in the USA.

Acceptability of GBS screening

Very little research has been reported on the acceptability to parents or health professionals of any of the means of preventing neonatal GBS infection. And, in contrast to other fields of antenatal screening, we know little about the psychological impact of GBS screening on mothers. One study,⁷⁵ conducted in Taiwan, measured attitudes to testing and the anxiety levels of women routinely tested for GBS between 35 and 37 weeks' gestation. This study found that, although state anxiety rose in women who screened positive, 1 week after delivery anxiety levels had returned to normal, and all mothers supported screening. An Australian study of women's attitudes to GBS and screening⁷⁶ showed that most women knew very little about GBS and those who underwent screening did so because it was part of routine care and was perceived to be better for the baby. A qualitative study⁷⁷ in Canada found that women did not feel that the low risk associated with GBS warranted the use of antibiotics, and they were also wary of taking a vaccine during pregnancy to prevent infection, should this become available.

Two surveys of health professionals' attitudes, knowledge and practice in relation to preventing neonatal GBS infection have been conducted. An Australian study⁷⁸ reported that only 56% of the obstetricians and 61% of the neonatologists who responded supported universal antenatal screening. Nearly all of those who rejected this approach supported antenatal screening by risk factors. However, a study⁷⁹ conducted in New Zealand reported that, although the lead maternity carers they surveyed believed that the prevention of neonatal infection was important and that they were confident in determining risk factors, none

correctly identified all high-risk factors and only 26% regularly discussed GBS with their clients.

The technology to allow rapid testing for GBS during labour has only recently been developed and so the acceptability of this form of screening for women and health professionals has yet to be assessed. However, there is a need to better understand both pregnant women's and health professionals' perceptions of GBS screening and the prevention of neonatal GBS infection during labour more generally. Any screening and infection prevention regime relies on the adherence of participants and health professionals.

Cost-effectiveness of GBS screening

Despite the contrasting guidelines for screening and prevention of neonatal GBS disease that exist for the UK and the USA, with the former recommending screening based on risk factors and the latter screening based on culture at 35–37 weeks' gestation, there was no cost-effectiveness evidence available to support either.

Recently, Colbourn *et al.*⁶⁹ carried out a study to determine the cost-effectiveness of prenatal strategies for preventing GBS and other bacterial infections in early infancy and to establish the expected value of further information. Their evaluation was carried out using a decision tree based largely on secondary data. They compared strategies of screening based on culture; screening based on the PCR rapid test; screening based on

risk factors; IAP; and vaccination. Their results suggested that screening based on risk factors or on the rapid test PCR was not a cost-effective strategy, and that vaccination was the most cost-effective option.

Given the recent developments in technology that have resulted in the development of the rapid test, a full economic evaluation based on data from the first primary study to evaluate its use in practice is required to ensure that decision-makers use available resources wisely.

Aims of the HTA project

The project was commissioned by the NIHR Health Technology Assessment Programme in 2002. The objective of the study was to evaluate the use of rapid tests for the detection of maternal GBS colonisation during labour and the prevention of neonatal GBS infection. PCR and OIA were chosen for investigation because these were the most promising of the rapid tests identified by the systematic review described in the previous section on the accuracy of rapid tests for GBS.

The project aimed to assess:

- the accuracy of intrapartum rapid PCR and OIA against the reference standard of enriched culture for maternal GBS colonisation
- the acceptability to mothers of rapid testing during labour

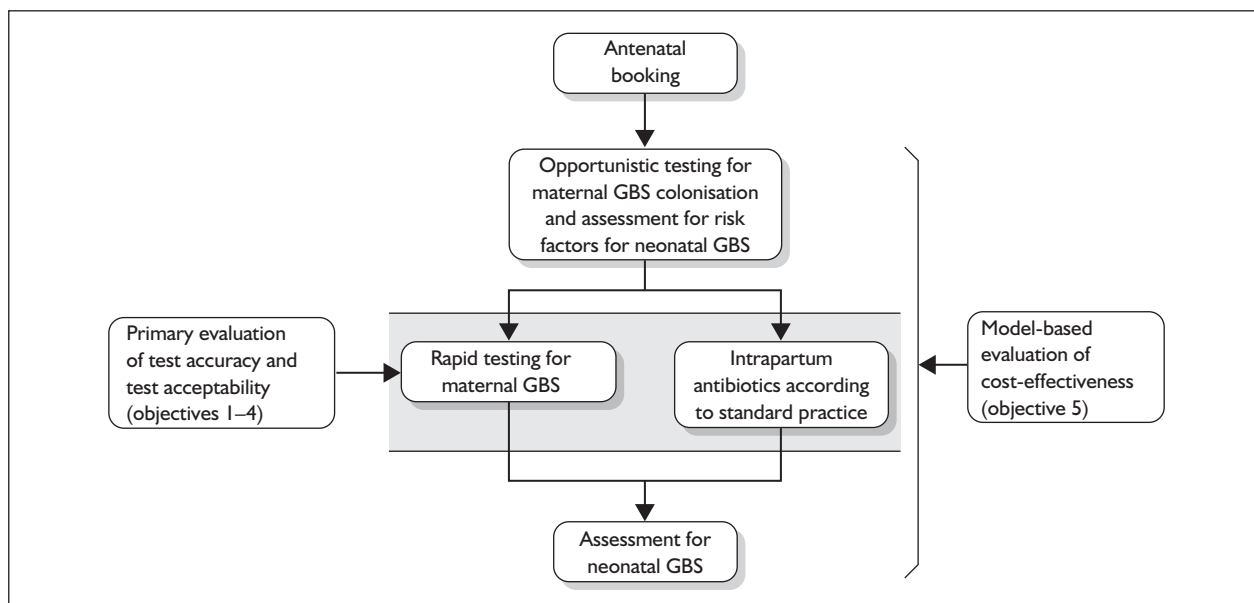


FIGURE 5 A brief outline of the HTA project and its clinical context.

- the cost-effectiveness of a rapid test-based screening and prevention strategy compared with existing or hypothetical strategies for EOGBS infection.

As outlined in *Figure 5* the key objectives were:

1. To develop PCR and OIA as rapid tests for GBS colonisation amongst women in labour using currently available technologies.
2. To determine the accuracy (sensitivity, specificity, predictive values) of PCR and OIA rapid tests for GBS colonisation of women in labour using selective enrichment culture as the reference standard.
3. To determine the variation in test accuracy according to (a) site of test swabs (vaginal and rectal) and (b) presence or absence of maternal risk factors.

4. To determine the acceptability of rapid testing for GBS colonisation among mothers of different ages and parity and from different age and ethnic groups.
5. To determine the cost and cost-effectiveness of rapid intrapartum testing for maternal GBS colonisation to prevent neonatal GBS disease, and to compare this with other strategies for screening and prevention.

The accuracy study was designed and managed in such a way as to meet the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) criteria for methodological quality.⁸⁰ Acceptability was assessed using a questionnaire survey and qualitative interviews. Cost-effectiveness analysis involved decision-analytic model-based economic evaluation.

Chapter 2

Diagnostic accuracy of polymerase chain reaction and optical immunoassay tests

Introduction

This chapter describes a test accuracy study to determine the accuracy of rapid tests for GBS colonisation of women in labour, using:

- population: mothers who plan to give birth vaginally who present in labour or have labour induced with a viable pregnancy
- index tests: PCR and OIA rapid tests on swabs obtained from the vagina and rectum
- reference standard: selective enrichment culture of swabs obtained from the vagina or rectum.

We compared the accuracy of index tests, determined whether tests were more accurate from vaginal or rectal swabs, evaluated whether test accuracy varied according to the presence or absence of maternal risk factors, and explored the determinants of neonatal colonisation.

Methods

Using recommended methods for diagnostic accuracy evaluation,⁸¹ an a priori protocol was developed with a classic test accuracy design. Research ethics committee (East London and the City Research Ethics Committee and local research ethics committees) and NHS trust research governance approval was obtained for recruitment in two large obstetric units, Birmingham Women's Hospital and King George Hospital, Ilford, serving a large socioeconomically and ethnically diverse population. These hospitals represented a busy specialised tertiary referral centre and a district general hospital respectively.

Study sample

All pregnant women booked for delivery at one of the two participating units, other than those electing for a Caesarean delivery, were approached for consent to be recruited into the study. Given the need to fully inform each woman about the study, to provide time for her to consider participation

and to avoid burdening her with information at the time of labour, a two-stage informed consent strategy was employed. Study information leaflets were given to all mothers at the time of their antenatal booking visit or at the mid-trimester scanning visit. Community midwives in the catchment areas for the hospitals were trained to reinforce the information provided and answer any questions that the women may have had.

Between 20 and 24 weeks, the provisional consent of the women was sought. Those agreeing in principle to provide swabs at labour were registered on a database, recording identifying and demographic details and expected date of delivery. Women's hand-held notes were marked with coloured stickers to identify whether they had provisionally consented or declined, thereby aiding identification of women to be reapproached for consent at presentation in labour. All women who had agreed in principle were asked to consent to participation when they presented to the labour ward with anticipated delivery or when they were admitted to the antenatal ward for induction of labour at later than 24 weeks' gestation. Women who had previously declined, who were undergoing elective Caesarean section or who were delivering very prematurely (≤ 24 weeks) were not approached for consent at labour.

Dilatation of the cervix, together with regular, progressively more frequent and painful contractions, indicates the onset of labour. Accuracy of tests for GBS colonisation may be altered by vaginal examinations performed before obtaining swabs for testing,^{82,83} therefore swabs were taken from the lower vagina and rectum before examination. Women who first presented in false labour, defined as no delivery within 7 days, were reapproached when they returned in labour. Swabs from false labours were not included in the accuracy analysis.

To minimise variation in the amount of bacteria on individual swabs, and to increase patient acceptance, a triple-headed swab was used to collect three samples simultaneously. This consisted

of three separate swabs bound together by two plastic bands (Medical Wire and Equipment, Corsham, Wiltshire). The swabs were obtained by the midwife or doctor assessing the woman at the time of admission to the antenatal or labour ward. A numbered testing kit was taken from stocks kept on the wards. These contained the swabs, the reagents for the rapid tests and a transport medium for the reference test, a data collection form and numbered stickers to identify the samples.

Separate triple swabs were used to sample first the lower vagina and then the rectum, when possible before any manual vaginal examination. Vaginal specimens for testing were obtained by gently rotating the swabs across the mucosa of the lower vagina. Rectal swabs were obtained by inserting the swabs through the anal sphincter and then gently rotating. The triple swab was then separated and each swab used for either one of the rapid tests or the reference test.

Index tests

The PCR and OIA rapid tests were performed separately on rectal and vaginal swabs using a standard operating procedure for point-of-care testing, using the Cepheid Smart GBS[®] kit and SmartCycler[®] system and Inverness Medical BioStar OIA STREP B[®] kits, respectively, described in Appendix 1. The swabs were tested on the antenatal or labour ward by trained midwifery assistants or by research staff (the majority of samples).

Reference tests

Laboratory-based selective enrichment culture of maternal and neonatal swabs was the gold or reference standard for verification of index test results. Swabs were inoculated into Lim broth with subculture onto tripticase soy agar after overnight incubation at 37°C.⁸⁴ The reference swab cultures were interpreted independently of the index tests by biomedical scientists. A password-restricted database prevented laboratory staff accessing index test results or neonatal outcomes and, as culture results were not available until later, maternity staff could not access laboratory data.

A swab from the neonate was also collected to determine transmission rates. The external ear canal was chosen on the basis of published studies showing it to be the most sensitive indicator of neonatal colonisation.^{85–87}

Management of labour and neonates

Apart from collection of swabs from mothers and their babies, all other aspects of patient management were entirely at the discretion of the local doctors. The PCR and OIA tests were performed on the labour ward, but the results were not provided to the midwife responsible for the woman. Treatment decisions were made solely according to established local guidelines, based on the presence or absence of risk factors:⁶¹ an incidental finding of GBS colonisation or GBS bacteriuria during pregnancy (GBS in the midstream urine specimen or vaginal swab tested opportunistically), previous baby with GBS disease, maternal fever (> 38°C) or chorioamnionitis, PROM (≥ 18 hours at term) and prematurity (< 37 weeks).

When IAP was given, the agents and dosage regimens were in accordance with the Green-top Guideline of RCOG.⁶¹ Briefly, intravenous penicillin, (3 g) given as soon as possible after the onset of labour and 1.5 g given 4-hourly until delivery, was the treatment of choice. Clindamycin 900 mg 8-hourly was used for women who were allergic to penicillin. Of the 122 women included in the final analysis who received antibiotics, none had any adverse reactions. Recent antibiotic therapy was also documented but was not a contraindication to inclusion in the study.

Sample size and power estimation

The literature that exists on sample size calculations for diagnostic studies provides a number of different approaches.^{88,89} Given the consequences of GBS infection it was felt that sensitivity below 75% would be unacceptable. Assuming a 'true' sensitivity of 90%, 70 cases would need to be recruited to refute reliably a sensitivity of less than 75% with 90% power at $p = 0.05$. This would require a total of 1400 participants assuming a 5% prevalence of maternal GBS colonisation, as shown in *Table 1*. The specificity could be estimated with greater reliability because of the large number of mothers without GBS in the study. This approach also produced a sample size estimate that was consistent with the sample size estimate of Alonzo *et al.*⁸⁹ for comparing the accuracy of tests. The assumption regarding disease prevalence was deliberately conservative, predicting rates of 5% or 10% compared with the pooled estimate of 13.6%,¹² so as not to compromise the power for estimating sensitivity.⁹⁰ A higher prevalence would increase the power for subgroup analysis for maternal colonisation.

TABLE 1 Power for the study of the accuracy of rapid tests for maternal group B streptococcus (GBS) colonisation with complete data on 1400 mothers

Assumptions		Prevalence of GBS							
		5% (70 cases of maternal GBS colonisation)				10% (140 cases of maternal GBS colonisation)			
		Power of the study				Power of the study			
'True' Sn	'True' Sp	80%	90%	80%	90%	80%	90%	80%	90%
95%	98%	85%	97%	83%	96%	89%	97%	87%	96%
90%	95%	78%	94%	75%	93%	82%	93%	80%	92%

Sn, sensitivity; Sp, specificity.

Analysis

An independent data monitoring committee (see Appendix 5) confidentially reviewed interim analyses on two occasions and recommended continuing recruitment until the end of funding as there was neither 'proof beyond reasonable doubt' that one test was sufficiently accurate nor evidence that might reasonably have been expected to influence clinical practice at any stage.

The main analysis of diagnostic accuracy of each index test for maternal GBS colonisation was computed as sensitivity (probability that the test is positive for GBS given maternal colonisation) and specificity (probability that the test is negative if the mother is not colonised), with 95% confidence intervals (CIs). Tests performed no more than 1 week before delivery were used for this primary analysis. Index test results from vaginal and/or rectal swabs were compared against the reference standard of vaginal and rectal laboratory culture. If either the vaginal or the rectal rapid test was positive, then the test was defined as positive for GBS colonisation. Conversely, both vaginal and rectal rapid tests had to be negative for the test to be defined as negative for GBS colonisation, and similarly for the reference standard. Index tests were additionally assessed against individual reference standards. To directly compare PCR against OIA, McNemar's test was used to test whether the PCR result was identical to the reference standard more frequently than was the OIA result, using a two-sided exact test. Additional analyses were carried out to compare the performance of index tests according to the site of swabs and the presence or absence of risk factors.⁶¹

Using multivariable logistic regression analysis, predictive probabilities for various combinations

of maternal risk factors and rapid test results were generated.⁹¹⁻⁹³ This approach evaluated the extent to which the findings of the index tests added value to the mother's history. The limitation associated with the regression approach lies mainly in its generalisability to other data sets or clinical practices. The recommended techniques, such as bootstrapping to enhance generalisability and estimate the amount of shrinkage, could be applied for model validation.^{94,95} The sample comfortably met the events per variable rule of 10:1 to avoid overfitting the models.⁹⁶⁻⁹⁸

We also studied the determinants of mother to child transmission. The effect of maternal risk factors, intrapartum antibiotics and rapid index test results on neonatal colonisation was evaluated with culture results of the neonatal ear swab as the outcome variable. To obtain a valid estimate of the association between the above determinants and neonatal colonisation, a multivariable logistic regression analysis was used. Most analyses were performed using SPSS version 14 or STATA version 8. The stratified analysis used the DerSimonian and Laird technique.⁹⁹

Results

Characteristics of participants

The first women were approached for participation in the study in March 2005 and the first woman was swabbed in June 2005. Recruitment to the study closed in January 2007 with 1418 women swabbed, 945 from Birmingham and 473 from Essex, as shown in *Figure 6*.

Results from 18 women were excluded from the analysis as delivery occurred later than 7 days after collection. A total of 10 women had false

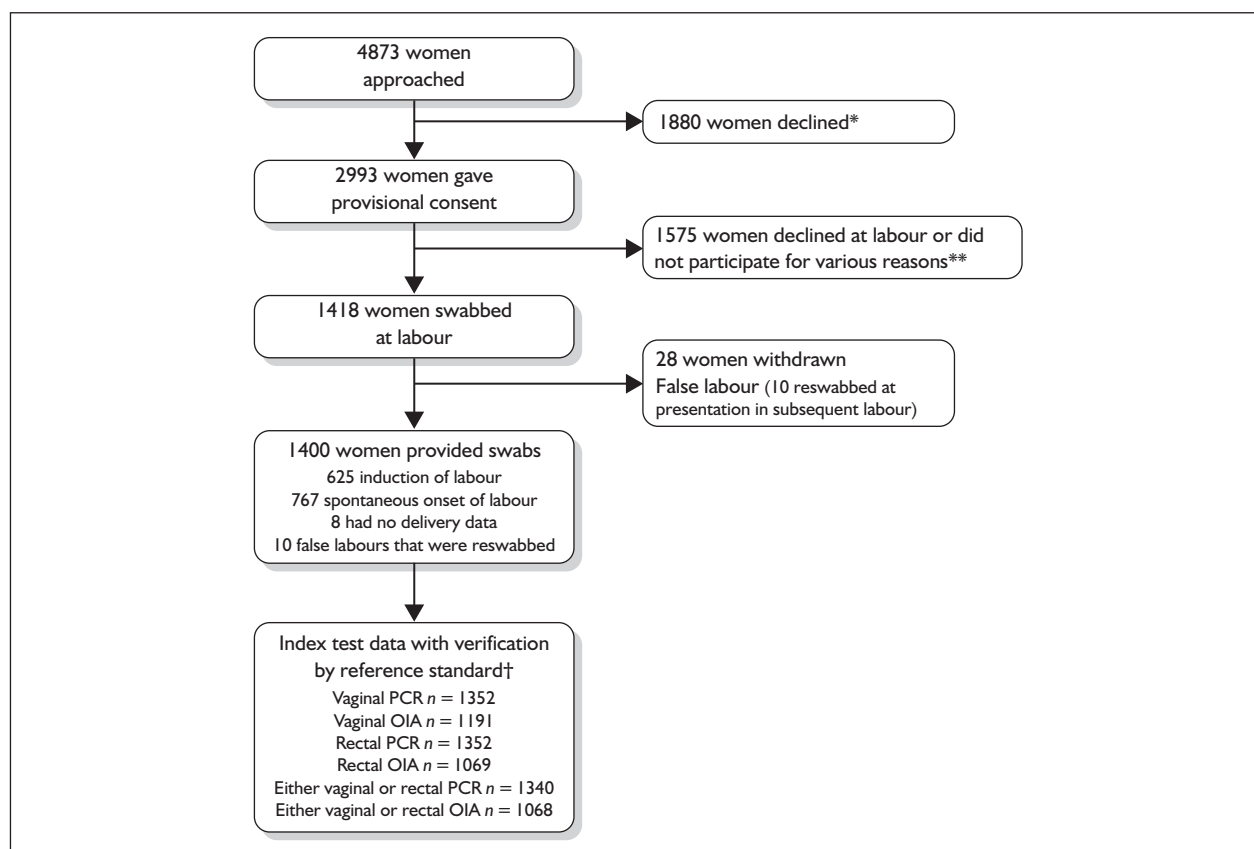


FIGURE 6 Recruitment of women into the diagnostic accuracy study (STARD flowchart). *No reason recorded 827 (44%), objected to rectal swab 73 (3.9%), objected to swabbing 241 (12.8%), planned Caesarean 132 (7.0%), delivery planned elsewhere/at home 17 (0.9%), insufficient English 111 (5.9%), did not want to participate in research 199 (10.6%), wanted no added intervention 77 (4.1%), family refused 38 (2.0%), worried if things went wrong/anxious about pregnancy 28 (1.5%), other reasons 137 (7.3%). Non-participants did not have to give a reason nor were midwives expected to record one. **No time to collect swabs 86 (5.5%), Caesarean section 94 (6.0%), delivered elsewhere or at home 56 (3.6%), language barrier 2 (0.1%), delivered after end of study 12 (0.8%), midwife not trained 8 (0.5%), no sticker on notes/denied giving provisional consent 314 (19.9%), pregnancy loss 8 (0.5%), mother too distressed 4 (0.3%), clinical complications at admission 58 (3.7%), missed for various unknown reasons 630 (40.0%), no reason identified 303 (19.2%). Midwives were not required to record reason. †Throughout study, colonisation or test results from either site were reported only if both vaginal and rectal swab results were available.

labours and were reswabbed on later presentation in labour; the second set of swabs were included in the analysis.

The characteristics of the women who participated in the study are shown in *Table 2*. Of the 1400 women recruited into the study, 308 (22.1%) had risk factors.

The mean gestational age was 40 weeks (standard deviation of 11.42 days for spontaneous deliveries and 10.84 days for inductions). About one-third of inductions were at gestational age ≤ 40 weeks. The average length of labour was 8 hours 15 minutes for spontaneous deliveries and 7 hours 20 minutes for induced deliveries.

Maternal GBS colonisation, as defined by a positive enriched culture result, was 15.5% from vaginal

swabs, 19.2% from rectal swabs and 21.2% if either result was positive. Colonisation rates varied depending on the presence or absence of risk factors, as shown in *Table 3*.

A total of 1291 baby ear cultures provided colonisation status, out of which 109 were culture positive. Of these, 99 were born from GBS-colonised mothers (as determined by either vaginal or rectal positive culture results), a neonatal colonisation rate of 8.4% of all deliveries and transmission rate of 36.3% of colonised women. There were 15 babies reported to have had an infection immediately postpartum, six of which were invasive infections. Of the invasive infections, three were diagnosed as EOGBS disease, all of whom recovered.

TABLE 2 Characteristics of women participating in an accuracy study of rapid intrapartum polymerase chain reaction (PCR) and optical immunoassay (OIA) tests for maternal group B streptococcus (GBS) colonisation

Number of women with demographic data	1 400
Age, mean (SD)	29.6 (5.9)
Parity, <i>n</i> (%)	
0	690 (52.6)
1	366 (27.9)
2	161 (12.3)
3	53 (4.0)
4	32 (2.4)
≥ 5	9 (0.7)
Ethnic group, <i>n</i> (%)	
White	868 (62.0)
Mixed	29 (2.1)
Asian	297 (21.2)
Black	145 (10.4)
Other	21 (1.5)
Not given	40 (2.9)
Number of women with risk factor data	1 394
No risk factor, <i>n</i> (%)	1 086 (77.9)
Any risk factor, <i>n</i> (%)	308 (22.1)
Single risk factor, <i>n</i> (%)	
Previous baby with GBS disease	4 (0.3)
GBS in current pregnancy	58 (4.2)
Maternal fever	12 (0.9)
PROM	171 (12.3)
Premature	18 (1.3)
Combination of risk factors, <i>n</i> (%)	45 (3.2)
GBS in current pregnancy and PROM	9 (0.6)
Premature and GBS in current pregnancy	1 (0.1)
Premature and PROM	17 (1.2)
Fever and PROM	15 (1.1)
Premature, GBS in current pregnancy and PROM	2 (0.1)
Premature, fever and PROM	1 (0.1)
Type of labour, <i>n</i> (%)	
Induction	625 (44.6)
Spontaneous	767 (54.7)
Type of delivery, <i>n</i> (%)	
Vaginal	856 (61.1)
Assisted vaginal	233 (16.6)
Caesarean	303 (21.6)

continued

TABLE 2 Characteristics of women participating in an accuracy study of rapid intrapartum polymerase chain reaction (PCR) and optical immunoassay (OIA) tests for maternal group B streptococcus (GBS) colonisation

Length of labour, <i>n</i> (%)	
< 4 hours	396 (28.4)
4–6 hours	325 (23.3)
7–9 hours	252 (18.1)
10–12 hours	185 (13.3)
≥ 13 hours	222 (15.9)
Not given	12 (0.9)

PROM, premature rupture of membranes.
Note: Parity was not recorded for 89 women and length and type of labour or delivery was not recorded for 8 women.

TABLE 3 Maternal group B streptococcus colonisation in the presence or absence of risk factors^a

Colonisation		Risk factor	
		Present	Absent
Vaginal	Present	67	147
	Absent	240	933
	Prevalence	21.8%	13.6%
Rectal	Present	79	188
	Absent	227	892
	Prevalence	25.8%	17.4%
Either	Present	89	205
	Absent	217	874
	Prevalence	29.1%	19.0%

a *n* = 1385 with complete culture and risk factor data. Culture or risk factor data was missing for 15 participants and rectal culture for a further two participants.

Assessment of test accuracy

Accuracy of PCR and OIA for maternal GBS colonisation

The accuracy of the rapid tests, compared against enriched culture, is shown in *Table 4*. PCR performed significantly better than OIA in all combinations of index and reference standard. Considering the PCR results, rectal PCR provided the most sensitive test for maternal GBS colonisation with a sensitivity of 71% (95% CI 66–76%), whereas specificity was 92% (95% CI 90–93%), identical to the specificity of vaginal PCR. Combining the PCR results from both sites increased the sensitivity to 84% (95% CI 79–88%) but with a lower specificity of 87% (95% CI 85–89%). This reflects the fact that, in the pooled test–reference accuracy measures, either test being positive defines GBS colonisation whereas both tests have to be negative for the participant to be considered negative for GBS colonisation.

To statistically compare the relative accuracy of OIA and PCR, the results of OIA and PCR compared with the reference standards were tabulated and McNemar’s test applied. All five combinations of rapid test and reference standard were significantly different, in favour of PCR being more accurate.

Variation in index test accuracy according to the presence or absence of maternal risk factors for GBS colonisation

There was variation in the specificity of the PCR rapid test with the presence or absence of risk factors for every combination of site and reference standard, except for vaginal PCR compared against either the vaginal or rectal reference standard. Variability was also observed in the sensitivity of vaginal OIA. In general, tests were more sensitive in those with risk factors and more specific in those without risk factors (*Table 5*). Other features

TABLE 4 Accuracy of rapid intrapartum tests of maternal group B streptococcus colonisation, according to site of swab

Reference standard, test site and index test	Number of tests				Accuracy measurement (95% CI)		p-value for difference PCR vs OIA ^a
	TP	FN	TN	FP	Sensitivity	Specificity	
Based on either vaginal or rectal enriched culture							
Vaginal PCR	171	122	975	83	0.58 (0.52–0.64)	0.92 (0.90–0.94)	<0.001
Vaginal OIA	88	165	860	77	0.35 (0.29–0.41)	0.92 (0.90–0.93)	<0.001
Rectal PCR	208	84	974	86	0.71 (0.66–0.76)	0.92 (0.90–0.93)	<0.001
Rectal OIA	150	80	498	341	0.65 (0.59–0.71)	0.59 (0.56–0.63)	<0.001
Either vaginal or rectal PCR	246	47	915	134	0.84 (0.79–0.88)	0.87 (0.85–0.89)	<0.001
Either vaginal or rectal OIA	171	66	476	375	0.72 (0.66–0.78)	0.56 (0.53–0.59)	<0.001
Based on vaginal enriched culture							
Vaginal PCR	148	64	1035	105	0.70 (0.63–0.76)	0.91 (0.89–0.92)	<0.001
Vaginal OIA	73	108	919	92	0.40 (0.33–0.48)	0.91 (0.89–0.93)	<0.001
Based on rectal enriched culture							
Rectal PCR	197	67	991	97	0.75 (0.69–0.80)	0.91 (0.89–0.93)	<0.001
Rectal OIA	140	70	508	352	0.67 (0.60–0.73)	0.59 (0.56–0.62)	<0.001

FN, false-negative; FP, false-positive; OIA, optical immunoassay; PCR, polymerase chain reaction; TP, true-positive; TN, true-negative.
^a McNemar's test used for comparison. Number of incomplete data pairs against vaginal reference was five for OIA, three for PCR; against rectal reference was four for OIA, five for PCR (see Appendix 3 for details).

TABLE 5 Sensitivity and specificity of rapid intrapartum tests for maternal colonisation according to the presence or absence of risk factors

Reference standard, test site and index test	Risk factor(s)	Number of tests					Sensitivity (95% CI)			Specificity (95% CI)		
		TP	FP	FN	TN	With risk factor(s)	No risk factors	p-value	With risk factor(s)	No risk factors	p-value	
Based on either vaginal or rectal enriched culture												
Vaginal PCR	Present	62	20	27	191	0.70 (0.59–0.79)	0.53 (0.46–0.60)	0.009	0.91 (0.86–0.94)	0.93 (0.91–0.94)	0.335	
	Absent	109	63	95	784							
Vaginal OIA	Present	37	16	41	167	0.47 (0.36–0.59)	0.29 (0.23–0.37)	0.005	0.91 (0.86–0.95)	0.92 (0.90–0.94)	0.775	
	Absent	51	61	124	693							
Rectal PCR	Present	64	29	25	182	0.72 (0.61–0.81)	0.71 (0.64–0.77)	0.865	0.86 (0.81–0.91)	0.93 (0.91–0.95)	0.002	
	Absent	144	57	59	792							
Rectal OIA	Present	48	60	24	92	0.67 (0.55–0.77)	0.65 (0.57–0.72)	0.755	0.61 (0.52–0.68)	0.59 (0.55–0.63)	0.745	
	Absent	102	281	56	406							
Vaginal or rectal PCR	Present	75	38	14	172	0.84 (0.75–0.91)	0.84 (0.78–0.89)	0.897	0.82 (0.76–0.87)	0.89 (0.86–0.91)	0.013	
	Absent	169	96	33	743							
Vaginal or rectal OIA	Present	54	63	18	89	0.75 (0.63–0.85)	0.70 (0.62–0.77)	0.438	0.59 (0.50–0.67)	0.56 (0.53–0.60)	0.617	
	Absent	110	300	47	387							
Based on vaginal enriched culture												
Vaginal PCR	Present	52	30	15	204	0.78 (0.66–0.87)	0.66 (0.58–0.74)	0.087	0.87 (0.82–0.91)	0.92 (0.90–0.93)	0.039	
	Absent	96	75	49	831							
Vaginal OIA	Present	32	21	28	181	0.53 (0.40–0.66)	0.34 (0.26–0.43)	0.012	0.90 (0.85–0.93)	0.91 (0.89–0.93)	0.484	
	Absent	41	71	80	737							
Based on rectal enriched culture												
Rectal PCR	Present	60	33	19	188	0.76 (0.65–0.85)	0.74 (0.67–0.80)	0.745	0.85 (0.80–0.90)	0.93 (0.91–0.94)	0.001	
	Absent	137	64	48	803							
Rectal OIA	Present	44	64	21	95	0.68 (0.55–0.79)	0.66 (0.58–0.74)	0.833	0.60 (0.52–0.67)	0.59 (0.55–0.63)	0.862	
	Absent	96	287	49	413							

FN, false negative; FP, false positive; OIA, optical immunoassay; PCR, polymerase chain reaction; TP, true positive; TN, true negative.

of the population and tests that could potentially influence the sensitivity and specificity of the test were considered and, although not prespecified, subgroup analyses were performed to investigate variability. Comparing the accuracy of the rapid tests with maternal colonisation between parous and nulliparous women showed no heterogeneity in the test characteristics (data not shown).

Predictive post-test probabilities

The logistic regression model used maternal GBS colonisation from either vaginal or rectal culture as the binary dependent variable. As shown in *Table 6*, the prior probability of maternal colonisation for women in this study was 21.7%, the prevalence according to vaginal or rectal culture. This increased to a post-test probability of 64.5% with a positive maternal PCR result from either the vaginal or the rectal swab, and reduced to 4.8% with a negative PCR result. When the presence or absence of risk factors was taken into account these post-test probabilities did not change substantially, despite a slight change in the prevalence in these groups.

TABLE 6 Estimated post-test probability of maternal group B streptococcus (GBS) colonisation combining results obtained from the vaginal or rectal rapid polymerase chain reaction (PCR) test with information available on maternal risk factors for GBS colonisation (n = 1340 with colonisation, PCR and risk factor data)

Maternal risk factor	Prior probability (%)	Estimated post-test probabilities (%)	
		Maternal PCR negative	Maternal PCR positive
Not considered	21.7	4.8	64.5
Absent (n = 299)	19.4	4.6	62.6
Present (n = 1041)	29.7	5.9	68.8

TABLE 7 Logistic regression estimates of the association between various factors and neonatal colonisation

Predictor variable	Simple regression		Multiple regression ^a	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Any maternal risk factor (present vs absent)	1.24 (0.78–1.96)	0.36	1.44 (0.80–2.62)	0.23
Intrapartum antibiotics (sufficient duration vs insufficient or not given)	0.57 (0.54–1.21)	0.23	0.22 (0.07–0.62)	0.004
Intrapartum antibiotics (sufficient or insufficient duration vs not given)	1.45 (0.48–2.73)	0.75	0.49 (0.18–1.34)	0.164
Intrapartum vaginal or rectal rapid PCR (positive vs negative)	26.9 (14.5–49.9)	< 0.001	29.4 (15.8–54.8)	< 0.001

PCR, polymerase chain reaction.

a Multiple logistic regression model with neonatal GBS colonisation determined by culture of neonatal ear swab as the binary dependent variable and any maternal risk factor; intrapartum antibiotics and intrapartum vaginal or rectal rapid PCR result as independent variables (see Analysis for details).

Determinants of neonatal GBS colonisation

The multivariable logistic regression model that evaluated the determinants of neonatal colonisation (*Table 7*) showed that the odds of having a colonised baby increased when an intrapartum rapid vaginal or rectal PCR test was positive but not when maternal risk factors were present. The odds were reduced by 78% with use of sufficient antibiotics (OR 0.22, 95% CI 0.07–0.62, $p = 0.004$), defined here as at least 4 hours between first dose and delivery. When any antibiotic provision was considered in the model the odds of neonatal colonisation were not reduced significantly.

Discussion

Summary of main findings

This is the largest test accuracy study comparing PCR and OIA rapid intrapartum tests for maternal GBS colonisation. Rapid PCR was more accurate than rapid OIA for the diagnosis of maternal GBS

colonisation. Index test results derived by using vaginal or rectal swab results were more sensitive than either test considered individually. The best accuracy was obtained using vaginal or rectal PCR rapid test results, giving a sensitivity of 84% (95% CI 79–84%) and specificity of 87% (95% CI 85–89%). The sensitivity and specificity of rapid tests varied according to the presence or absence of maternal risk factors. The PCR test results significantly altered the post-test probability of maternal colonisation and were determinants of neonatal colonisation. Knowledge of risk factor status did not alter this substantially.

Strengths and limitations of methods

The validity of our findings relies on the quality of the study. We complied with and reported all criteria for a high-quality test accuracy evaluation.¹⁰⁰ We minimised methodological bias and explored for variability in estimation of test accuracy. We ensured that the index tests and reference standard were performed independently and interpreted blind to each other. There was a very high proportion of index test verification by reference standard (over 96% for PCR). We investigated the effect of spectrum bias by collecting data on characteristics of the sample and assessing variability across various spectra. A sample size calculation was performed to ensure that the study had sufficient power to exclude a clinically unacceptable accuracy and the study recruited to that target. We are therefore confident that our findings concerning superiority of PCR over OIA are robust.

With regard to the generalisability of the findings of our study, one needs to explore the extent to which the observed results can be expected to be replicated in routine care. To begin with, the study sample may not be truly representative of a typical UK maternity population. Several differences were noted compared with other studies on the subject and compared with findings in the general population, as outlined in the following section. Test results may not be as consistently and rapidly obtained when the tests are employed in a point-of-care situation and conducted by staff providing usual care to labouring women. Indeed, the median times taken to obtain rapid test results within the study were 80 minutes and 35 minutes for PCR and OIA, respectively, excluding collection of the swab, compared with 65 minutes and 18 minutes in the time and motion study (see Appendix 6). Although

in our study research staff performed the majority of the PCR tests, they did so in batches, with results usually obtained after delivery, as the test technology precluded samples being processed as they were received in real time. New developments in PCR platforms will eliminate most of the preparatory steps and allow multiple samples to be tested on demand, although the accuracy of such systems will need to be validated. Caution is needed when considering the applicability of our findings, which may be moderated by local circumstances such as the availability of staff and their capability to perform tests on demand (see Chapter 5, Strengths and limitations, and Appendix 2 for further discussion).

Interpretation of findings

In this section we seek to interpret our data and to explore the clinical relevance of the findings. We have briefly discussed the validity of the evidence and the extent to which the results can be applied to usual care. Here we compare our findings with other evidence, to put them into context.

Concerning the representativeness of our study sample, the patients recruited comprised only about 10% of the total number of women delivering in the two centres and there is evidence to suggest that the sample was not representative. Proportionally more white women were recruited (e.g. 62% in the study compared with 55% of the total deliveries at Birmingham Women's Hospital), following a national trend in research in which South Asians are under-represented¹⁰¹ but which may also reflect a lack of acceptability of the procedure or other barriers to participation. Variations in the reasons for non-participation between ethnic groups will be discussed in Chapter 3 (see Declining to take part in the study during pregnancy). Only 2.7% of pregnancies included in the study delivered prematurely, lower than the national average of 7.1% of all live births in England and Wales.¹⁰² This may be because staff tended to avoid asking this group for consent, to avoid additional anxiety for the mother. Conversely, a greater proportion of women in the study were undergoing induction of labour than the population average, 45% compared with approximately 18% (Birmingham Women's Healthcare NHS Trust, 2007, personal communication), as midwives had more time to obtain consent and take samples on the antenatal ward. Emergency Caesarean sections are also over-represented in the study sample, making up 21.6%

of the deliveries compared with a national rate of 13.5%;¹⁰³ although this excess will not influence maternal GBS colonisation it might have an effect on neonatal colonisation. A lower proportion of study participants had risk factors than in other reported studies – 22% compared with 28.9% in the study of Colbourn and Gilbert¹² – possibly because fewer premature births were recruited.

The rate of maternal GBS colonisation in this study, at 21.2% for combined vaginal or rectal colonisation, is higher than that reported in a recent meta-analysis of UK studies (14%; 95% CI 10–18%),¹² although the latter includes studies reporting vaginal colonisation only. The risk of neonatal GBS colonisation given maternal colonisation is similar to the pooled estimate from a meta-analysis of six UK studies.¹² The study sample was too small to compare EOGBS disease rates with those in previous reports.

Women were not offered IAP on the basis of the index test results but were treated according to RCOG and Health Protection Agency guidelines,^{61,62} although not comprehensively. The administration of antibiotics to the mother may eliminate GBS colonisation and prevent transmission, but only if a sufficient dose is received before delivery. Multiple logistic regression demonstrated that a positive rapid PCR test does significantly increase the odds of neonatal colonisation, whereas IAP significantly reduces the odds if given for at least 4 hours before delivery. There were insufficient cases of EOGBS disease to determine predictors of disease.

We found that the accuracy of the rapid tests was not as high as that previously reported. The highest levels of accuracy came from combining the results from vaginal and rectal swabs, for both PCR and OIA. However, this was considerably lower than the pooled estimates from a meta-analysis of all previous studies.³⁵ That reported a pooled sensitivity and specificity of 97% for PCR and a pooled sensitivity of 55% and a pooled specificity of 96% for OIA. This may be because, with more robust methodology, we avoided an overestimation of accuracy associated with review bias, a feature prevalent in previous studies.¹⁰⁴

Updating the meta-analysis to include our study reduces the pooled estimates for PCR, with a new pooled sensitivity of 90% (95% CI 88–93%) and a pooled specificity of 92% (95% CI 91–94%). For OIA the pooled sensitivity increased to 63% (95%

CI 57–97%) and the pooled specificity decreased to 79% (95% CI 78–80%). Although meta-analysis weights the individual study data according to the precision of the study, it does not take into account the methodological weaknesses of the included studies. With PCR, for example, six of the seven previous studies did not blind the results of the index test from the interpreter of the reference standard, which may have biased verification. The accuracy of PCR, when considering samples from both sites, compares favourably with that of screening by culture of swabs taken at 35–37 weeks' gestation. A meta-analysis demonstrated a pooled sensitivity of 76% and a pooled specificity of 95% for culture-based tests.⁶⁹

The prevalence of maternal GBS colonisation varies with the site of swabbing, with rates highest when both vaginal and rectal swabs are considered. This is mirrored by increasing sensitivities, with the lowest sensitivity being observed using vaginal swabs and the highest observed when vaginal and rectal swabs are combined. Specificities do not vary as much with prevalence. It is unclear as to why there is this variation. The mucosal environment of the vagina and rectum are different, especially with regards to pH, and GBS has obviously adapted to both sites, but perhaps colonisation is heavier in the rectum and therefore more likely to be collected by swabbing. It is apparent that rectal swabbing is necessary to maximise sensitivity but the acceptability of this procedure is an issue, which will be discussed in detail in Chapter 3.

There is also variation in accuracy in the presence or absence of maternal risk factors, with sensitivities generally higher in the presence of risk factors and specificities higher in their absence. Differences are generally small and there is no general pattern as to which test–reference combinations are statistically different. So, although there is some variation in test characteristics according to presenting characteristics, the impact is not significant. This is also observed in the logistic regression model to calculate post-test probabilities, in which the presence or absence of risk factors did not significantly alter the outcomes.

Neonatal GBS infection is the reference standard of real interest, although it was not possible to use the neonatal ear swab as a reference standard here as antibiotics were prescribed to mothers on the basis of maternal risk factors, leading to a reduction in the rates of transmission from mother to baby. Any treatment that alters the verification of the

reference standard after the index test inherently biases the study. Risk factors were not a significant factor in the prediction of neonatal colonisation, whereas a positive result from PCR was predictive, again reflecting their respective sensitivities.

Recommendations for the economic model

The decision-analytic model needs to consider estimates of probabilities obtained in this study, other estimates available for other screening tests or strategies and patient preferences. One of the key issues concerning screening tests in this project is that, if available, effective interventions are relatively simple, inexpensive and without a high risk of harm or side effects (to both mother and child). In this situation high test sensitivity is more important than high specificity, because the cost of false-negative results is likely to be high in relation to the costs incurred in treating all index test-positive results. In this regard, PCR is superior to OIA in our study, although both tests tend to have higher specificity than sensitivity. It seems unlikely that consideration of maternal risk factors will improve the cost-effectiveness of rapid test-based screening as it adds little to the post-test predictive values. It appears that index tests obtained from a combination of vaginal and rectal swabs would perform best, but the acceptability of rectal swabbing needs to be evaluated (see Chapter 3). A threshold analysis (see Chapter 4, Deterministic sensitivity analysis) will be required to determine the levels of sensitivity and specificity required to make rapid testing cost-effective in

the prevention of EOGBS disease with currently available preventative treatment.

Implications for practice

Given the generally low sensitivity of the OIA test system evaluated, a practical recommendation for clinicians when making a decision about the use of intrapartum antibiotics is not to use OIA as a test for maternal GBS colonisation. If an intrapartum rapid test is to be considered for practice, PCR appears currently to be the most accurate test, although the current commercially available test may not have sufficiently high sensitivity to be cost-effective (see Chapter 4).

Recommendations for research

The evaluation of a test system should follow a robust design for test accuracy studies with sufficient power to estimate test sensitivity over and above that achieved by the PCR tests used in this study.

The extent to which cost-effectiveness threshold analysis can be developed to inform sample size estimation in test accuracy studies needs to be investigated. The minimum duration of IAP during labour and the relative importance of individual risk factors in predicting maternal colonisation can be estimated from this data set and validated in future larger studies. More work and discussion is required to establish the models of independent monitoring of test accuracy studies and stopping rules.

Chapter 3

Evaluating the acceptability of rapid testing during labour

Introduction

When any new antenatal or neonatal screening programme is introduced, consideration should be paid to the acceptability of screening to parents and the psychological impact of the screening procedure. Antenatal screening for a variety of conditions has become routine and all women in this study will have been offered tests for conditions in the fetus and, to a lesser extent, themselves during pregnancy. The extensive literature on antenatal screening and neonatal screening suggests that, although it is highly acceptable to most parents,¹⁰⁵ it can have a psychological cost regardless of the test results.^{106,107} Raising the subject of screening in itself may affect the psychological well-being of parents and affect their relationship with their baby.¹⁰⁸ Worry seems largely unrelated to the tests that a woman undergoes or to her knowledge of such tests.¹⁰⁹ Although the views and motivations of pregnant women and mothers have been sought and studied, such views are seldom sought before the technology is introduced.¹¹⁰

Most of the evaluation of screening in the literature is of screening for a serious condition in the fetus, which may entail decisions about termination¹⁰⁷ (e.g. Down syndrome), the neonate¹¹¹ (e.g. congenital hearing impairment) or the mother, which may also affect the baby¹¹² (e.g. HIV status). Screening for GBS therefore differs from most antenatal and neonatal screening in that the condition is tested in the mother but, although it is common, it has little impact on the health of mothers themselves.

The most obvious parallel in terms of the way in which neonates will be affected by GBS infection is antenatal HIV testing to try to prevent infection being transmitted to babies during birth. Before routine testing was offered in the UK uptake was low, and, although it is now much higher, there are concerns that uptake is still low in those who perceive themselves not to be at risk¹¹³ and amongst those who are at greater risk,¹¹⁴ possibly because of the stigma attached to the HIV-positive status and perceived impact on the mother.

Although some stigma may be attached to having GBS infection, the lack of impact of the condition on mothers may make GBS screening more acceptable. The nature of the screening procedure, and the perceived relevance of the test to individuals who may not see themselves as being at risk, are likely to be more important factors in GBS screening. However, giving pregnant women more information about GBS and offering screening may in itself raise anxiety.

There has been very little research on testing for, and treating, GBS infection during pregnancy from the mother's perspective. As discussed in Chapter 1, several routine and risk-based test and treatment regimes are in place. Nevertheless, evidence of the uptake and impact of these remains scarce. One study,⁷⁵ conducted in Taiwan, measured the anxiety levels of women routinely tested for GBS between 35 and 37 weeks' gestation and attitudes to testing. This study found that, although state anxiety rose in women who screened positive, 1 week after delivery anxiety levels had returned to normal. Furthermore, all women in the study were extremely positive about screening.

An alternative to screening for GBS antenatally is to treat those who are objectively at risk. As discussed in the introductory chapter there are five risk factors that can be shown to affect the likelihood of having GBS and transmitting the infection to the baby: prematurity, intrapartum fever, PROM, a previous baby with GBS disease and GBS colonisation in the current pregnancy. If a universal screening programme is to succeed, it is obviously important that women with these risk factors find the screening acceptable. However, it is equally, if not more, important that screening is acceptable to women who would be unlikely to be detected by a strategy to treat those at greatest risk. It is also important to remember that, whereas risk factors can be objectively classified, women themselves may be unaware that they are regarded as at risk or conversely may feel themselves to be at risk when they are not, for example if GBS was detected in a previous pregnancy. For those who feel themselves to be at risk, testing for GBS is more salient and their views on the information

given about it, the testing procedure and the role of testing during labour in routine care may vary from those for whom GBS is less salient. All of these factors will influence the extent to which any screening or treatment programme is acceptable to the target population of the programme, which will in turn affect uptake.

Aims

The aims of this part of the study were:

- to investigate the reasons why women declined to take part in this screening study when they were approached during pregnancy, and whether the reasons were linked to demographic characteristics
- to assess the acceptability to newly delivered women of rapid testing for GBS during labour and whether any variation observed was linked to demographic characteristics or psychological variables
- to develop an understanding of midwives' perceptions of rapid testing for GBS and the detection and prevention of transmission of GBS more generally.

Methods

Participation in the study

Data were collected on the mothers who declined to take part in the study when they were first approached, during pregnancy. This consisted of basic demographic details and reasons for declining to take part. The reasons for declining were entered in free text and subsequently coded for analysis.

Acceptability of rapid testing Questionnaire development

The acceptability of testing was assessed using a questionnaire designed for the study but incorporating standardised measures. The questionnaire was designed on the basis of the literature on antenatal and neonatal screening and diagnosis. To maximise face and content validity of the questionnaire it was developed by one of the investigators (HMP), a health psychologist, in consultation with the research team, which included experienced midwives and obstetricians. Measures of acceptability and patient satisfaction are often problematic because of a lack of variability in what are often very positive evaluations.¹¹⁵ In this study attempts were made

to address this issue by specifically targeting different aspects of the screening process and making the questions as concrete and relevant to the participants' own experiences as possible. The draft questionnaire and information about the study were presented to recently delivered mothers on a postnatal ward and tested in face-to-face cognitive interviews. Interviewees were asked, as far as they felt able, to complete the questionnaire and comment on the style and comprehensibility of the questions, the relevance of the topics covered, whether any issues had been omitted and the overall length and readability of the questionnaire. As a result the questionnaire was modified slightly; some repetitive questions were removed and key questions on GBS screening were moved to the beginning of the questionnaire.

The questionnaire had four main parts:

1. Satisfaction with information provided on GBS, the study and treatment (10 items).
2. The procedure for obtaining samples, specifically the comfort and embarrassment of swab-taking (5 items).
3. Perceptions of the introduction of rapid screening as part of routine care. The areas addressed in this third section were largely hypothetical for participants in this study, as the results were not made available to them on the labour ward and they were not treated on the basis of the results. These areas would require further investigation if assessments of accuracy and cost effectiveness suggest that rapid testing for maternal GBS should be introduced into routine perinatal care.
 - i. How confident they were that test results could be kept confidential.
 - ii. How confident they were that the test would be carried out competently.
 - iii. Freedom to make a choice about treatment.
 - iv. Using rapid testing as a basis for treatment.
 - v. Preference for rapid testing over professional assessment of risk.
 - vi. Whether they would recommend it to others (usually a reliable measure of satisfaction).¹¹⁵
 - vii. How important it would be to them to have the test.
4. The final part of the questionnaire measured psychological variables that may be associated with the impact or acceptability of screening:
 - i. State anxiety – the 6-item version of the State-Trait Anxiety Inventory (STAI) was included.¹¹⁶ This was developed for similar populations and has been widely used in screening studies.¹¹⁷

- ii. Illness perceptions in the baby – illness perceptions of the identity, severity, chronicity and controllability of GBS infection were measured using an adapted version of the Brief Revised Illness Perceptions Questionnaire¹¹⁸ (8 items).
- iii. Perceptions of GBS in the mother – two items were included to measure whether women thought that they would have symptoms of GBS, and how concerned they would be about having GBS themselves.
- iv. Health anxiety – the 7-item short version of the Whiteley Index (Whiteley-7)¹¹⁹ was used to measure health anxiety.
- v. Health anxiety for the baby – the Whiteley Index was adapted to measure the mother's health anxiety towards the baby during pregnancy.

All questions were answered on a forced choice scale, most with five possible responses. At the end of the questionnaire participants were invited to make any further comments they wished on any aspect of the study, their treatment or their own or their baby's health. These comments were not systematically analysed but extracts are used to illustrate some points in the results.

The questionnaire was distributed on the postnatal ward to be completed within 24 hours of birth to limit recall bias. However, if the questionnaire was not completed before discharge, mothers were encouraged to take it home and return it later.

Acceptability to midwives

The acceptability to midwives of rapid testing for GBS as a routine procedure was investigated in two focus groups with midwives who had taken part in the study (FG1 and FG2), before the results were communicated to them. The focus groups were held in a meeting room in the hospital after the participants had finished a shift, and refreshments were offered. The groups were facilitated by one of the investigators (HMP), supported by

one of the research midwives (EE). Both focus groups consisted of six midwives with a range of experience; a further person arrived late at the first group but did not contribute to the discussion. All participants were assured of confidentiality, asked to respect the confidentiality of the rest of the group and informed that the session would be recorded. Issues explored included general perceptions of GBS, perceptions of the efficacy of testing, costs to staff in terms of time and effort involved, perceived benefits of testing, professional views on the impact on mothers and alternatives to rapid testing. The discussions of the focus groups were recorded on a digital recorder, professionally transcribed and analysed using qualitative thematic analysis.¹²⁰ A summary of the characteristics of the participants is given in *Table 8*.

Results

Declining to take part in the study during pregnancy

Table 9 indicates that the proportions of different ethnic groups and age groups among those declining to participate in the study when first approached during pregnancy differed from the proportions among those who eventually participated in the study. There was a significant association between ethnic group and declining to take part ($\chi^2 = 249.90$, $p < 0.001$) and between age and declining to take part ($\chi^2 = 149.04$, $p < 0.001$). There was a higher proportion of South Asian women, particularly those of Pakistani origin, in the women who declined. (Here, and in the remainder of this chapter, women are referred to by their self-reported ethnic origin for the sake of brevity, for example women whose ethnic origins are Pakistani may be referred to as Pakistani women. This is not intended to imply anything about their status or citizenship, which was not recorded.) There was also a higher proportion of younger women in the sample who declined to take part.

TABLE 8 Employment characteristics of the participants in the focus groups (all midwives)

Focus group 1	Focus group 2
On delivery suite	On delivery suite and postnatal wards
On delivery suite and community midwife	On delivery suite
On delivery suite, previously a community midwife	On delivery suite and postnatal wards
On delivery suite	On delivery suite
On delivery suite, previously on postnatal wards	Student midwife on placement on delivery suite
On delivery suite and postnatal wards	On delivery suite

TABLE 9 Proportions of different ethnic groups and age groups among those who declined to take part in the study during pregnancy and among those who participated in the study

	Declined (n = 1880), n (%)	Participated (n = 1400), n (%)
Ethnic groups		
White (British and Irish)	677 (36.0)	816 (58.3)
White (other)	52 (2.8)	53 (3.8)
Other	233 (12.4)	98 (7.0)
Asian (Indian)	187 (9.9)	107 (7.6)
Asian (Pakistani)	470 (25.0)	131 (9.4)
Asian (Bangladeshi)	87 (2.6)	26 (1.9)
Black (Caribbean)	43 (2.3)	49 (3.5)
Black (African)	86 (4.6)	80 (5.7)
Not given	45 (2.4)	40 (2.9)
Age group		
≤ 20 years	248 (13.6)	93 (6.6)
21–25 years	506 (27.7)	243 (17.4)
26–30 years	537 (29.3)	399 (28.5)
31–35 years	365 (19.9)	427 (30.5)
36–40 years	155 (8.5)	189 (13.5)
≥ 41 years	19 (1.0)	48 (3.4)
Not given	50 (3.0)	1 (0.07)

Reasons for declining to take part in the study during pregnancy

Table 10 indicates that, although no reason was recorded for the majority of participants declining to participate in the study, those who did express a reason declined to take part for both a general unwillingness to participate in the research and specific reasons relating to procedural aspects of participating (swabs) and other worries concerning their pregnancy. The reasons for declining during pregnancy varied by ethnicity ($\chi^2 = 296.93$, $p < 0.001$) and age group ($\chi^2 = 146.73$, $p < 0.001$). No pattern was discernable in the proportions of each group giving no reason for declining. However, white British and Irish women were over-represented in those who declined because they objected to the swabs, particularly rectal swabs, and amongst those who planned to have a Caesarean section or deliver somewhere other than in the participating hospital. Pakistani women and 'other white' women were over-represented amongst those who had insufficient English to participate. South Asian, particularly Pakistani, women were over-represented amongst those who objected to the vaginal swab, but this was a very small number overall.¹⁹ Younger women were more likely to decline to take part because they objected to either or both of the swabs.

Acceptability of rapid testing for GBS during labour

Data management and analysis

Before analysis, scoring on some items was reversed to ensure a similar coding scheme, such that a higher score indicated a higher level of agreement with the question statement. An analysis of the internal consistency of the 10 questions on the information given to participants on GBS and the study showed that this was very high (Cronbach's $\alpha = 0.93$). Therefore, all analyses have been conducted on the mean score for the 10 items to give an overall score for satisfaction with the information provided; a score of 1 represents the most negative response and 5 the most positive response. Similarly two questions on testing as part of routine care, on the confidentiality of results and the test being carried out properly, showed high consistency (Cronbach's $\alpha = 0.91$) and were combined. All other questions in the first three parts of the questionnaire were analysed separately.

For the purposes of analysis, parity, age group and ethnic group were used as independent variables. Level of risk was calculated from the risk factors identified at an earlier stage of the study. Women were classified according to their level of risk of transmitting GBS during birth as high (previous

TABLE 10 Reasons for declining to participate in the study during pregnancy

Reason	%
No reason	44.0
Objected to rectal swab	3.9
Objected to vaginal swab	1.0
Objected to both swabs	11.8
Planned Caesarean	7.0
Delivery elsewhere/home	0.9
Insufficient English	5.9
Did not want to participate	10.6
Wanted no added intervention	4.1
Family refused	2.0
Worried about things going wrong	0.3
Anxious about pregnancy	1.2
Other	7.3

GBS baby and/or GBS colonisation in current pregnancy), medium (delivering prematurely, intrapartum fever, PROM) or low (no recognised risk factors).

Mean scores were analysed using one-way analysis of variance (ANOVA), with post hoc Bonferroni comparisons. The relationship between demographic and psychological variables and the various measures of acceptability and satisfaction were explored using multiple regression analyses. When dependent variables were not normally distributed, a log or square transformation was applied as appropriate. For all analyses *p*-values of less than 0.05 are reported as statistically significant, except for the regression analyses, in which a more stringent level of 0.01 was used.

The responses of women who had returned their questionnaires while still in hospital were compared with the responses of those who had returned them at a later date. No significant differences were found between the two groups and so the complete data set was included in the analyses. A total of 1044 questionnaires were returned completed. Many had missing items and these were excluded from the relevant analyses.

Participation in the study and anxiety

The mean state anxiety score for the sample as a whole who completed the STAI (*n* = 946) was 34.12 (95% CI 33.34–34.89). This is slightly lower than the values obtained in previous studies of pregnant women¹¹⁶ and screening for GBS

during pregnancy,⁷⁵ but within the normal range as indicated by the normative values in the STAI manual (35.2 for working adult women, 36.17 for 19- to 39-year-old women). In a one-way ANOVA, no significant differences in state anxiety were found between those women who tested positive for GBS during pregnancy and those who either were not tested or were tested and displayed a negative result (*p* > 0.05). This indicates that the levels are similar to the postpartum results of women tested for GBS in the study by Cheng *et al.*⁷⁵

Overall acceptability with information, testing procedure and rapid testing as routine care

Table 11 shows that the average ratings of the study and rapid testing for GBS are high. However, although scores are still above the midpoint on the scale, women who participated found vaginal swabbing more comfortable and less embarrassing than rectal swabbing. There is also some indication that some women would prefer a doctor or midwife to treat them on the basis of their professional judgement of the risk, rather than undergoing a rapid test.

Satisfaction with information

One-way ANOVA revealed no significant differences in the mean scores for acceptability of information between women of different parity, ethnicity or age. Table 11 shows that the participants' evaluation of the information given to them was quite high. However, this needs to be considered with some caution as women reported in the open comments at the end of the questionnaire that the information had been given to them so long before that they could not remember it well:

Not entirely clear about study because have forgotten what midwife explained. She did explain but I have forgotten a lot of it.

Felt it was a long time ago I was given information on study and had forgotten most of it when it came to filling out form.

Some women interpreted the illness perception questionnaire as a test of knowledge rather than a test of perceptions of GBS, and gave that as a reason for not completing it: 'Sorry that I can't complete the detailed GBS info – I haven't got the leaflet with me and can't remember.'

TABLE 11 Average levels of satisfaction with the information given, acceptability of the testing procedure and acceptability of rapid testing as part of routine care

	<i>n</i>	Mean score (95% CI)
Overall satisfaction with information: 1 = very unsatisfied; 5 = very satisfied	1043	4.01 (3.97–4.05)
Testing procedure		
Happiness with the way that swabs were taken: 1 = very unhappy; 5 = very happy	1043	4.42 (4.38–4.46)
Comfort of vaginal swab: 1 = very uncomfortable; 5 = very comfortable	1044	4.04 (3.99–4.10)
Comfort of rectal swab: 1 = very uncomfortable; 5 = very comfortable	1041	3.74 (3.67–3.81)
Embarrassment with vaginal swab: 1 = not at all embarrassed; 5 = very embarrassed	1032	1.33 (1.29–1.36)
Embarrassment with rectal swab: 1 = not at all embarrassed; 5 = very embarrassed	1022	1.64 (1.59–1.69)
Rapid test as part of routine care		
Confident results would be confidential and test carried out properly: 1 = very unconfident; 5 = very confident	1036	4.41 (4.37–4.44)
Free to make treatment choice: 1 = very unconfident; 5 = very confident	1024	4.32 (4.31–4.40)
Go ahead with treatment on basis of test: 1 = definitely not; 5 = yes definitely	1029	4.61 (4.57–4.63)
Prefer professional judgement to rapid test: 1 = definitely not; 5 = yes definitely	1013	3.05 (2.97–3.13)
Would recommend test to others: 1 = definitely not; 5 = yes definitely	1027	4.32 (4.27–4.37)
Importance of having test: 1 = very unimportant; 5 = very important	1024	4.41 (4.38–4.46)

Acceptability of the testing procedure

There were five questions on the testing procedure relating to the samples taken for testing. As there was not sufficiently high internal consistency in the responses to the five questions to assume that they were measuring the same construct, they have each been analysed separately. Again, as *Table 11* shows, the acceptability of the swabs was generally high. As one participant said:

The last thing I was worried about was the swabs. I'd just started contractions and since everyone's heads were going to be peeking down there anyway ... I didn't worry.

Parity

There was a significant main effect of parity on the acceptability of vaginal swabs [$F(3, 969) = 3.253$, $p = 0.015$]. Post hoc analysis indicated that those with three or more previous pregnancies experienced less discomfort with the vaginal swabs than the other groups. There was no other significant parity-related effect.

Ethnicity

There was a significant main effect of ethnic group on comfort with vaginal swabs [$F(8, 1035) = 4.353$, $p < 0.001$]. Post hoc analysis indicated that this was due to the white British and Irish participants

reporting greater levels for comfort than either Indian or Pakistani participants ($p = 0.001$ and $p = 0.029$ respectively). A similar analysis on levels of embarrassment experienced when the vaginal swabs were taken revealed a significant effect of ethnic group [$F(8, 1023) = 7.143$, $p < 0.001$]. Post hoc analysis indicated that white British and Irish participants experienced lower levels of embarrassment than either Indian or Pakistani participants ($p = 0.037$ and $p < 0.001$ respectively). Those classified as 'white other' showed lower levels of embarrassment than Pakistani women ($p = 0.011$) and black Caribbean women experienced lower levels of embarrassment than Indian or Pakistani participants ($p = 0.009$ and $p < 0.001$ respectively).

There was also a significant main effect of ethnic group on overall acceptability of the way that samples were taken [$F(8, 1034) = 4.139$, $p < 0.001$]. Post hoc analyses indicated that white British and Irish participants were happier with sample taking than either Indian or Pakistani participants ($p = 0.028$ and $p < 0.001$ respectively) (*Table 12*).

Age

In general, the younger age groups found the test procedure less acceptable than the older age groups. Specifically, there was a significant effect in terms of embarrassment with vaginal swab

taking [$F(5, 1026) = 7.219, p < 0.001$] in that the two groups aged 25 years or less showed greater embarrassment than the older groups aged from 26 to 40 years ($p < 0.001$). There was also a significant effect of age on embarrassment with rectal swab taking [$F(5, 1016) = 3.538, p = 0.004$]. Post hoc analysis indicated that the participants in the group aged from 21 to 25 years showed greater levels of embarrassment than the participants in the two groups aged from 26 to 35 years ($p = 0.015$ and $p = 0.001$ respectively). There was also a significant effect of age on comfort with vaginal swabs [$F(5, 1038) = 2.665, p = 0.021$]. Post hoc analysis indicated that the youngest group (20 years and under) reported significantly lower levels of vaginal comfort than the oldest group (41 years and over) ($p = 0.046$) (Table 12).

Acceptability of rapid testing as part of routine care

A series of questions was designed to measure women's perceptions of using rapid testing as part of routine care. For the women in this study

these questions were hypothetical as they were not treated on the basis of the results of the tests and, indeed, were not for the most part made aware of the results. Table 13 summarises the results on the acceptability of rapid testing for GBS as part of routine care.

Parity

Analyses revealed no significant effect of parity on questionnaire responses on the acceptability of rapid testing in routine care.

Ethnicity

There was a significant difference between ethnic group in terms of confidence that the test would be carried out correctly and would be confidential [$F(8, 1027) = 7.912, p < 0.001$]. Post hoc analysis revealed that white British and Irish participants expressed greater levels of confidence than Indian, Pakistani and black African participants ($p = 0.015, p < 0.001$ and $p < 0.001$ respectively).

There were significant differences in the confidence of women that they would be free to make a choice

TABLE 12 Acceptability of testing procedure by parity, ethnicity and age [mean score (95% CI)]

	Overall acceptability of swabs	Comfort with swabs		Embarrassment with swabs	
		Vaginal	Rectal	Vaginal	Rectal
Ethnic group					
White (British and Irish)	4.50 (4.45–4.56)	4.15 (4.08–4.22)	3.75 (3.65–3.84)	1.26 (1.22–1.30)	1.61 (1.55–1.67)
White (other)	4.42 (4.21–4.64)	4.09 (3.72–4.46)	4.03 (3.63–4.43)	1.21 (1.04–1.38)	1.52 (1.23–1.80)
Mixed and other	4.37 (4.23–4.51)	4.00 (3.76–4.24)	3.72 (3.48–3.97)	1.38 (1.24–1.52)	1.67 (1.45–1.88)
Asian (Indian)	4.24 (4.11–4.36)	3.71 (3.59–3.92)	3.68 (3.45–3.90)	1.48 (1.34–1.61)	1.67 (1.49–1.84)
Asian (Pakistani)	4.16 (4.00–4.31)	3.81 (3.61–4.01)	3.63 (3.42–3.85)	1.62 (1.45–1.79)	1.87 (1.68–2.06)
Asian (Bangladeshi)	4.35 (4.04–4.67)	3.88 (3.41–4.36)	3.71 (3.20–4.21)	1.53 (1.21–1.85)	1.71 (1.35–2.06)
Black (Caribbean)	4.46 (4.25–4.67)	4.26 (3.96–4.55)	3.91 (3.54–4.28)	1.06 (0.98–1.14)	1.62 (1.33–1.90)
Black (African)	4.32 (4.17–4.48)	3.81 (3.58–4.04)	3.66 (3.39–3.93)	1.43 (1.26–1.60)	1.58 (1.38–1.79)
Not given	4.30 (4.08–4.54)	3.82 (3.47–4.17)	3.79 (3.45–4.13)	1.50 (1.26–1.74)	1.66 (1.36–1.95)
Age group					
≤ 20 years	4.34 (4.12–4.56)	3.78 (3.46–4.09)	3.37 (3.00–3.73)	1.55 (1.32–1.78)	1.76 (1.48–2.03)
21–25 years	4.37 (4.28–4.47)	3.92 (3.79–4.05)	3.63 (3.47–3.79)	1.51 (1.41–1.61)	1.86 (1.72–2.00)
26–30 years	4.39 (4.31–4.47)	4.10 (4.00–4.20)	3.87 (3.75–3.99)	1.32 (1.25–1.39)	1.60 (1.51–1.69)
31–35 years	4.47 (4.41–4.54)	4.07 (3.97–4.16)	3.74 (3.62–3.86)	1.27 (1.22–1.32)	1.56 (1.48–1.64)
36–40 years	4.41 (4.30–4.52)	4.03 (3.88–4.19)	3.67 (3.47–3.86)	1.23 (1.15–1.30)	1.60 (1.47–1.74)
≥ 41 years	4.53 (4.32–4.73)	4.36 (4.12–4.61)	4.06 (3.71–4.40)	1.22 (1.08–1.36)	1.64 (1.37–1.91)

TABLE 13 The acceptability of rapid testing for group B streptococcus as part of routine care by ethnicity and age [mean score (95% CI)]

	Confidence in test procedure	Free to make treatment choice	Happy to have treatment on basis of test	Prefer professional judgement	Recommend test to others	Importance of having test
Ethnic group						
White (British and Irish)	4.51 (4.46–4.55)	4.44 (4.39–4.49)	4.65 (4.61–4.70)	2.89 (2.80–2.99)	4.36 (4.30–4.43)	4.44 (4.39–4.50)
White (other)	4.33 (4.16–4.50)	4.19 (3.92–4.45)	4.47 (4.23–4.71)	3.30 (2.91–3.69)	4.38 (4.10–4.65)	4.31 (4.08–4.54)
Mixed and other	4.38 (4.23–4.52)	4.33 (4.17–4.45)	4.71 (4.58–4.85)	3.03 (2.76–3.31)	4.42 (4.24–4.60)	4.50 (4.35–4.65)
Asian (Indian)	4.26 (4.14–4.39)	4.22 (4.08–4.35)	4.54 (4.41–4.66)	3.34 (3.09–3.60)	4.20 (4.01–4.39)	4.32 (4.16–4.48)
Asian (Pakistani)	4.13 (3.98–4.28)	4.13 (3.97–4.29)	4.41 (4.23–4.58)	3.53 (3.28–3.80)	4.02 (3.83–4.22)	4.29 (4.17–4.41)
Asian (Bangladeshi)	4.44 (4.12–4.77)	4.25 (3.84–4.66)	4.41 (4.00–4.82)	3.82 (3.37–4.28)	4.29 (3.94–4.65)	4.29 (3.94–4.65)
Black (Caribbean)	4.38 (4.21–4.56)	4.32 (4.10–4.55)	4.50 (4.24–4.76)	3.15 (2.69–3.60)	4.44 (4.18–4.70)	4.59 (4.39–4.78)
Black (African)	4.09 (3.89–4.29)	4.20 (4.01–4.38)	4.64 (4.46–4.82)	3.40 (3.06–3.75)	4.24 (3.99–4.49)	4.39 (4.19–4.60)
Not given	4.25 (4.06–4.44)	4.23 (3.98–4.47)	4.53 (4.29–4.77)	2.97 (2.52–3.42)	4.22 (3.89–4.55)	4.35 (4.13–4.58)
Age group						
≤ 20 years	4.35 (4.17–4.54)	4.29 (4.08–4.51)	4.60 (4.39–4.82)	2.94 (2.60–3.28)	4.33 (4.08–4.59)	4.38 (4.18–4.57)
21–25 years	4.38 (4.28–4.47)	4.33 (4.23–4.44)	4.54 (4.43–4.65)	3.39 (3.23–3.56)	4.29 (4.16–4.42)	4.37 (4.27–4.57)
26–30 years	4.42 (4.34–4.49)	4.34 (4.27–4.42)	4.63 (4.57–4.70)	3.09 (2.94–3.24)	4.34 (4.25–4.43)	4.44 (4.36–4.52)
31–35 years	4.40 (4.33–4.46)	4.35 (4.28–4.43)	4.60 (4.53–4.66)	2.93 (2.79–3.06)	4.28 (4.20–4.37)	4.41 (4.34–4.48)
36–40 years	4.46 (4.37–4.55)	4.43 (4.32–4.54)	4.67 (4.58–4.77)	2.87 (2.67–3.08)	4.40 (4.27–4.53)	4.51 (4.42–4.61)
≥ 41 years	4.46 (4.26–4.65)	4.39 (4.20–4.58)	4.56 (4.31–4.80)	3.29 (2.83–3.75)	4.26 (3.95–4.56)	4.25 (3.93–4.57)

about treatment [$F(8, 1015) = 3.683, p < 0.001$] and how happy women would be to receive treatment on the basis of the test results [$F(8, 1020) = 2.439, p = 0.013$]. Post hoc analysis indicated that, for all of these variables, white British and Irish participants expressed more positive attitudes than Pakistani participants ($p < 0.05$).

Similarly there was an effect of ethnicity on preference for being treated on the basis of professional judgement rather than on the basis of the test result [$F(8, 1004) = 5.203, p < 0.001$], with white British and Irish participants preferring to be treated on the basis of the test than Pakistani women ($p < 0.05$).

Finally, there was a difference according to ethnic group in willingness to recommend the test to others [$F(8, 1018) = 2.287, p = 0.020$]. Again, this effect was due to white British and Irish women being more willing to recommend the test than Pakistani women ($p < 0.05$) (Table 13).

Age

There was a significant age group-related difference in the preference for treatment on the basis of professional judgement [$F(5, 1006) = 4.152, p = 0.001$] (Table 13). Post hoc analysis indicated that the 21- to 25-year-old group expressed less confidence in the test than the 31- to 35-year-old group and the 36- to 40-year-old group ($p = 0.001$ and 0.004 respectively). There were no other significant effects of age group.

Acceptability of rapid testing by risk status

Satisfaction with information

One-way ANOVA revealed no significant differences in mean scores for the acceptability of information given by level of risk. These results are shown in Table 14.

Acceptability of the testing procedure

A significant main effect of risk group was found for embarrassment when the rectal sample was taken [$F(2, 1018) = 4.510, p = 0.011$], with the medium-risk participants reporting significantly lower levels of embarrassment than the low-risk participants ($p = 0.016$) (Table 15). There were no other significant effects observed for acceptability of the test procedure by risk level.

Acceptability of rapid testing as routine care

Significant effects of risk group were observed for having treatment on the basis of the rapid test [$F(2,$

$1026) = 3.157, p = 0.043$] and the importance of having the test [$F(2, 1021) = 5.287, p = 0.005$]. Post hoc analysis revealed that the high-risk participants were more happy to have treatment on the basis of the test than the medium-risk participants ($p = 0.043$) and that the high-risk participants felt that having the test was more important than the low-risk participants ($p = 0.006$). There were no other significant effects (Table 16).

Analyses of demographic and psychological predictors of acceptability

As indicated above, six psychological variables were measured in the questionnaire: state anxiety, health anxiety, health anxiety for the baby, negative illness perceptions of GBS in the baby, perceived likelihood of symptoms of GBS (in mother) and concern about GBS (in mother). These were included, together with the demographic variables analysed above, in a series of multiple regression analyses to see whether the psychological variables explained variation in the acceptability measures. The results are reported in the following sections for completeness, with the caveat that, although several of the regression models were statistically significant, they explained very little of the variance. Also, many cases had to be dropped from these analyses because of missing data on one or more of the variables.

Information

The regression model for acceptability of information was significant but $r^2 = 0.03$. [$F(6, 849) = 4.03, p = 0.001$]. Higher satisfaction with information was associated with lower state anxiety ($\beta = -0.11, p = 0.002$), more positive illness perceptions ($\beta = -0.10, p = 0.007$) and belief that the mother would experience few symptoms of GBS herself ($\beta = -0.09, p = 0.018$). It is possible that state anxiety could have been lowered by satisfactory information provision; however, given the direction of the other effects, it seems more likely that the state anxiety measurement is a reflection of general feelings about birth and new motherhood.

Acceptability of the testing procedure

In the regression equation for embarrassment with the vaginal swab, $r^2 = 0.03$ [$F(6, 849) = 3.57, p = 0.002$]. The only significant predictor was state anxiety ($\beta = 0.13, p < 0.001$). Similarly, for the rectal swab $r^2 = 0.02$ [$F(6, 849) = 3.13, p = 0.005$; state anxiety $\beta = 0.10, p = 0.004$]. In both cases higher anxiety was associated with higher reported

TABLE 14 Satisfaction with information given by risk level

Risk level	Mean score (95% CI)
High	3.88 (3.69–4.07)
Medium	4.00 (3.90–4.09)
Low	4.02 (3.97–4.07)

embarrassment. None of the regression analyses for acceptability was significant.

Acceptability of rapid testing as routine care

Regression analyses on whether mothers would prefer testing to professional judgement gave $r^2 = 0.05$ [$F(6, 849) = 7.39, p < 0.001$]. Two variables were significant predictors: lower illness perceptions of GBS in the baby ($\beta = -0.19, p < 0.001$) and higher health anxiety in the mother ($\beta = 0.15, p = 0.001$). The regression equation for using the rapid test as the basis for treatment gave $r^2 = 0.03$ [$F(6, 849) = 4.85, p < 0.001$]. Significant predictors were belief that the mother would experience few symptoms of GBS herself ($\beta = -0.12, p = 0.001$) and less concern by the mother about having GBS herself ($\beta = -0.15, p < 0.001$). The final significant regression equations were for the perceived importance of having the test, $r^2 = 0.06$ [$F(6, 849) = 8.75, p < 0.001$], and whether mothers

would recommend the test to others, $r^2 = 0.02$ [$F(6, 849) = 3.17, p = 0.004$]. As in the previous analysis, significant predictors were belief that the mother would experience few symptoms of GBS herself ($\beta = -0.10, p = 0.005$, and $\beta = -0.09, p = 0.014$ respectively) and lack of concern by the mother about having GBS herself ($\beta = -0.20, p < 0.001$, and $\beta = -0.11, p = 0.004$ respectively).

Psychological variables and ethnicity

It is possible that some of the differences observed between different ethnic groups reflect differences between groups in the psychological variables measured. To explore this possibility one-way ANOVAs were carried out for the main ethnic groupings: white British and Irish; South Asian (Indian, Pakistani and Bangladeshi); black Caribbean and black African. These revealed significant effects of ethnicity on state anxiety [$F(3, 825) = 7.00, p < 0.001$], health anxiety [$F(3, 881) = 12.17, p < 0.001$], health anxiety for the baby [$F(3, 889) = 2.89, p < 0.04$] and illness perceptions of GBS in the baby [$F(3, 807) = 6.01, p < 0.001$]. Post hoc analyses showed that South Asian women reported significantly higher state anxiety, health anxiety and health anxiety for the baby than white British and Irish women. Black African women perceived GBS infection in the baby as significantly less dangerous than white British or black Caribbean women. Various types of anxiety were predictive of the acceptability of the testing

TABLE 15 Acceptability of testing procedure by risk level [mean score (95% CI)]

Risk level	Overall acceptability of swabs	Embarrassment with swabs		Comfort with swabs	
		Vaginal	Rectal	Vaginal	Rectal
High	4.43 (4.25–4.61)	4.20 (3.98–4.42)	3.80 (3.51–4.09)	1.31 (1.16–1.45)	1.75 (1.52–1.98)
Medium	4.43 (4.33–4.52)	4.01 (3.88–4.14)	3.64 (3.47–3.80)	1.37 (1.29–1.46)	1.78 (1.66–1.89)
Low	4.42 (4.37–4.47)	4.04 (3.98–4.11)	3.76 (3.68–3.84)	1.32 (1.28–1.36)	1.59 (1.54–1.65)

TABLE 16 Acceptability of rapid testing as routine care by risk level [mean score (95% CI)]

Risk level	Confidence in test procedure/ confidentiality	Free to make treatment choice	Happy to have treatment on basis of test	Prefer professional judgement	Recommend to others	Importance of having test
High	4.36 (4.21–4.40)	4.22 (4.05–4.40)	4.81 (4.69–4.92)	2.87 (2.46–3.29)	4.56 (4.36–4.76)	4.67 (4.54–4.81)
Medium	4.40 (4.32–4.48)	4.35 (4.25–4.45)	4.57 (4.48–4.67)	3.24 (3.07–3.42)	4.32 (4.20–4.43)	4.46 (4.37–4.55)
Low	4.42 (4.37–4.46)	4.37 (4.32–4.42)	4.60 (4.56–4.65)	3.02 (2.93–3.11)	4.30 (4.24–4.36)	4.39 (4.34–4.44)

procedure and some aspects of the acceptability of rapid testing in routine care, which match the differences observed between white British and Irish women and South Asian women in that higher anxiety, as seen in South Asian women, is associated with lower levels of acceptability, also observed in South Asian women. However, the low levels of variance explained by the regression models for psychological variables suggests that there are other more important cultural factors that underlie the ethnic differences.

Acceptability of rapid testing by salience of GBS

The final set of analyses on the questionnaire data looks at the acceptability of rapid testing by the salience of GBS for women. Women were classified either in the high-salience category (previous baby with GBS disease and/or GBS colonisation in current pregnancy and/or GBS colonisation during a previous pregnancy and/or received antibiotics during labour for GBS) or in the low-salience category (all other cases including all those with delivery-related risk factors but who were not given antibiotics). Note that this classification is conservative in that not all women who had GBS during a previous pregnancy would have had this noted, and there would be other reasons for GBS being more salient, for example having a friend with experience of GBS.

Levels of state anxiety according to salience of GBS to the participant

One-way ANOVA revealed a significant difference in the level of state anxiety reported according to the salience of risk [$F(1, 925) = 5.985, p = 0.015$], with participants reporting higher levels of state anxiety when the risk of GBS was salient to them (mean 36.5, 95% CI 34.2–38.9) than when it was not (mean 33.7, 95% CI 32.9–34.5). This suggests that the classification has some validity.

Satisfaction with information

One-way ANOVA revealed no significant differences in the mean scores for acceptability of information given according to salience of risk ($p > 0.05$).

Acceptability of the testing procedure

Participants for whom GBS was not salient reported higher levels of embarrassment at having the rectal swabs taken [$F(1, 1003) = 5.452, p = 0.020$]. There were no other significant effects.

Acceptability of rapid testing as routine care

Those participants for whom GBS was salient reported lower levels of confidence that the test would be performed correctly and would be confidential [$F(1, 1016) = 7.216, p = 0.007$], as well as less confidence that they would be free to make treatment choices [$F(1, 1005) = 7.093, p = 0.008$]. These participants, however, reported that they felt that the test was more important than those for whom GBS was not salient [$F(1, 1004) = 7.023, p = 0.008$]. There were no other significant effects. These results are summarised in *Table 17*.

Acceptability to midwives

Several inter-related themes emerged from the two focus groups. Although there was some discussion of the experience of taking part in the study per se, prompted by the questions posed by the facilitator, the participants mainly used their experiences of the study to illustrate and validate their reflections on testing and treating GBS more broadly.

Experience of the study

All of the participants felt that the study had added significantly to their workload, especially the associated paperwork:

And it was very difficult in triage because obviously there's only one midwife, and when you've got like 10 women ... I don't think it's actually the swabs, I think it was the paperwork more than ...

FG1

There was a general feeling that the midwifery assistants were not helpful in taking on the extra work involved, and this linked with the midwives' perceptions of their own roles as professionals on the delivery suite (see below):

It made the workload in triage a little bit more, and sometimes when it's heaving you haven't got time to take your swabs and do your paperwork. And I know there's midwifery assistants there to help, but they weren't any good.

FG2

However, the groups felt that the study had been well thought out and that the researchers were aware of their problems, particularly the research midwife:

TABLE 17 Acceptability of rapid testing as routine care by salience level [mean score (95% CI)]

	Confidence in test procedure/ confidentiality ^a	Free to make treatment choice ^a	Happy to have treatment on basis of test	Prefer professional judgement	Recommend to others	Importance of having test ^a
Salient	4.28 (4.19–4.37)	4.21 (4.10–4.32)	4.64 (4.54–4.74)	3.07 (2.84–3.29)	4.37 (4.23–4.50)	4.56 (4.47–4.65)
Not salient	4.43 (4.39–4.47)	4.37 (4.32–4.43)	4.61 (4.57–4.65)	3.05 (2.97–3.13)	4.31 (4.26–4.36)	4.40 (4.36–4.45)

a Difference between the two groups significant ($p < 0.01$).

The cards that you carried in your pocket were a good, very good idea. Because ... if you're doing it on the wards you've got that card that you can refer to.

FG1

There were mixed views on the importance of the study and this links into the next theme:

But I think the fact that you can get organ damage and stuff like that, I mean that was ... that was quite a high motivating factor for me ... And I think for the mums as well.

FG1

Importance of preventing GBS transmission

Discussion of the importance of preventing GBS infection centred around two issues: the commonness of babies becoming ill and the seriousness of the illness in neonates. Only one participant had direct experience of nursing an affected baby, and few had been aware of babies they had delivered becoming infected. In general, the midwives did not feel that they were well informed about GBS, and some comments on the risk factors suggested that there was a belief that risk factors went beyond those considered here, to include issues of personal hygiene. The rarity of the condition in their own experiences tempered the importance that they placed on preventing it and ultimately their willingness to endorse rapid testing: 'My initial impression is that it's not such a big problem considering the numbers of women we have here compared to the admissions to the neonatal unit with GBS.' (FG2).

Those who felt that GBS was too rare to consider another task being added during delivery (rapid testing) marshalled health economics to support their stance: 'If you look at the cost, would it not be very expensive to introduce routine testing and then treating?' (FG2).

However, to counter this there were examples produced of even rarer conditions that are prevented through midwifery interventions: 'I suppose when you think that we give vitamin K to every baby when they ... when haemolytic disease is only one in 10,000.' (FG1).

And when the seriousness of the condition was discussed there was more support for preventative measures: 'I mean you have to think if it saves a baby's life, even if it's one a year, then it's worth it because that's somebody's baby.' (FG1).

The nature of the measures preferred is raised in another theme. There was some scepticism at the notion that any method would eliminate GBS transmission:

with 6000 deliveries and if only three babies get admitted, I think that that incidence will remain because ... there are a number of women who will fall through the net.

FG2

The midwives felt that the study was more successful in recruiting than it might have been at other times because of the raised profile of GBS in the media:

G: 'And I think fortunately it's ... wasn't there something in one of the soaps or something like that?'

H: 'Coronation Street.'

K: 'Did they lose a baby?'

H: 'She lost a baby with strep meningitis.'

G: 'And I think it was sort of quite newsworthy for a while, wasn't it? So it wasn't like ... I think if you'd have done it a couple of years before then nobody would have heard of it.'

FG2

Acceptability of taking swabs during labour

The midwives generally did not feel that taking vaginal swabs during labour was problematic, as it was an extension of their normal procedures. However, even then they would not allow the study to interfere with care for women who were, for example, in severe pain. This was the main reason they gave for women not being included in the study who had previously not declined: 'If like you know, they're fitting or bleeding or ... it would then not be appropriate, would it? In any emergency situation it would not.' (FG2).

However, their views on rectal swabbing were entirely negative. This was something they thought of as outside their normal role and as unpleasant:

There's a big difference between the two different orifices. FG2

I hated doing them to be honest ... Women's hygiene is completely different but the anal one, especially when I was hungry, oh lord! Ohhhh. FG2

They also felt that the women they were taking swabs from found the rectal swabs less acceptable:

They understood to an extent what the swabs were for and what the purpose was behind the study, but when you actually said to them, 'I need to put this swab ... here' [all laugh] ... it was then like, 'oh'.

Practical issues in rapid testing as part of routine care

The main practical problem that midwives identified was the time taken to get the results of the test as it is currently run.

In 20 minutes, you could have seen two women or started two women, or in 40 minutes you'd have three women in each room. Do you know what I mean; you'd be multitasking in that time. FG2

There's women that come in who are almost fully dilated, you just wouldn't bother then I have to say, because by the time you get a cannula and the IV antibiotics in ... FG2

The test would only work in practice if it could be carried out quickly:

We'll get good at putting forms in! [laughter] I think it's like you say, that the paperwork would not ... it wouldn't be that. It would be something you quickly did wouldn't it? I presume it would just be a swab that you then look at in however many minutes or something like that. FG1

You've got to be standing there and looking at your watch really. You wouldn't want something like that because if you went back into your room and you forgot for half an hour. FG1

This was linked to the issue of the shortage of staff to take the sample and process it:

And who would be doing it? When you send up an urgent full blood count you have to ring up an hour later because you still haven't got a result, even though you've put urgent on. FG1

However, there were also problems associated with other methods of prevention. For screening in late pregnancy, communication of results was seen as the main problem, although it was recognised that information technology is advancing and this might improve: 'We'll all have little Blackberries in our pocket that we just take out. But I mean it is a difficulty that we have accessing notes out of hours.' (FG1).

Professional role of the midwife on the delivery suite

The midwives in both groups felt that if testing during labour was to become part of routine practice then they should be the people with the professional responsibility to carry out the testing. They would not want others, for example midwifery assistants, to take that role. There was concern that if a case was missed then they would be blamed, but they saw themselves as the most appropriate group to be held accountable:

I'm not meaning to put anyone down, I think that midwives are more used to considering ethical and legal obligations of it being done accurately and appropriately. FG1

... if you take a swab, could you just go and get the ... you know what I mean, you take ownership of it. You take ownership of that

woman's result and then it doesn't get lost or mislaid.

FG1

Some welcomed testing during labour as an extension of their skills and responsibilities: 'And if you can get that result yourself, it's like every other investigation that you would do for somebody in labour.' (FG1).

Perceptions of the rapid test in relation to other methods of preventing GBS transmission

The two groups differed somewhat in their perceptions of the role of testing during labour, although both groups thought it should be available. The first group was more positive towards rapid testing as the sole method of screening; the second group expressed a slight preference for rapid testing to be used as a backup for routine screening late in pregnancy or treatment on the basis of risk factors:

I still think in labour, because then you can do every ... nobody gets missed then, do they.

FG1

I would think that I would like to see a mixture/a combination of the two, because I think you can't dismiss the risk factors because they're there and they're evident, and we know that they have an impact on a woman's health and her baby's health. But likewise, as F was saying, ... where you know, she's never had a swab taken and you know, we're totally oblivious, then you know, we need to have something in place whereby they're not missed.

FG2

And once the practical issues were overcome they could see testing during both pregnancy and labour fitting into their normal practice:

It's like triple tests isn't it, or anything like that, you get the consent. And if they don't want the test they don't have the test. If they have the test, it's positive and they don't want the IV antibiotics, they don't have them.

FG1

Most of the midwives were unsure about the value of treating women on the basis of risk factors alone. They felt that this would lead to too many women being treated inappropriately as well as too many women at risk being missed. However, one participant was in favour of using this method,

as long as there were clear guidelines based on a checklist.

Problems with prophylactic antibiotics for GBS

Both groups of midwives were opposed to universal administration of antibiotics to prevent GBS transmission. One group would not even discuss the possibility and only discussed antibiotic treatment in relation to those women who tested positive or who were judged to fall into a risk category. They also felt that the pregnant women themselves would be wary of unnecessary treatment, because of antibiotic resistance and the general fears of taking medication during pregnancy that might affect the baby:

Women actually will come back to you the next week, book themselves in and say, 'Look, I wasn't happy, I haven't taken them.' Women will not just take antibiotics willy-nilly now.

FG1

I mean you don't just have carbon footprints now; you have antibiotic footprints.

FG1

In addition there was concern that administration of intravenous antibiotics would interfere with normal birth plans, which would be unpopular with both delivering women and midwives. These concerns about unnecessary antibiotic administration led to more positive evaluations of accurate testing during pregnancy and labour.

Discussion

Summary of the findings on acceptability

There is no evidence that taking part in the study raised anxiety levels, as anxiety levels were similar to or lower than those recorded in other studies of antenatal and perinatal screening. The responses of women who took part in the study were generally very positive. They were satisfied with the provision of information, although there is some doubt that they had retained the information. They did not find the process of swabbing unpleasant, although vaginal swabs were more acceptable than rectal swabs. This was echoed in the midwives' comments; they did not see rectal swabs as part of their normal role and saw it as unpleasant. The taking of swabs was also a major reason why women declined to take part when first approached.

The responses to questions about rapid testing and treatment for GBS during labour becoming part of routine care were again generally positive. Participants were confident that the test would be carried out properly and were happy to be treated on the basis of results. There was a marginal preference for rapid testing over treatment on the basis of risk assessment. Most women felt that the test was important and would recommend it to others. There is little evidence that the perceptions of participants were related to whether or not they fell into a high-risk category, except that high-risk participants felt that the test was more important and would be happier to be treated on the basis of the test result.

The ethnic group from which women came was related to the acceptability of testing and the uptake of the study. This was mainly due to differences between white British and Irish women and South Asian, particularly Pakistani, women. South Asian women were less happy with the sampling procedure and with the prospect of rapid testing as part of routine care; they were more likely to prefer professional judgement as the basis for treatment. South Asian women were also over-represented in the group of women who declined to take part in the study at all. Age was also related to perceptions of the test, with the younger age groups (below 25 years) being less positive than older participants, regardless of parity level.

Analyses of the links between acceptability and the psychological variables measured showed that none accounted for a large percentage of the variance in the data. State anxiety was the most predictive in that women who were more anxious were less satisfied with the information given and less happy with the way that samples were taken. Women's perceptions of GBS in themselves were related to the importance that they placed on the test, using the test as a basis for treatment and whether they would recommend it to others. However, the psychological predictors of whether women said that they would prefer to be treated on the basis of professional judgement than the test were more negative perceptions of GBS in the baby and lower health anxiety for their own health.

There were some differences found between women for whom GBS should be salient and those who had no recorded experience of GBS. The high-salience group was more anxious and they reported lower levels of embarrassment with the rectal swabbing. However, the main differences came in relation to rapid testing as part of routine care. The high-salience group was less confident that the test

would perform correctly and be confidential, and that they would be free to make treatment choices. These participants, however, reported that they felt that the test was more important than those for whom GBS was not salient.

The focus groups with midwives found that they were also generally positive about rapid testing but had some reservations from their experiences of the study. They feared that the high prevalence of GBS colonisation in women may lead to overtreatment and unnecessary interference in birth and overprescription of antibiotics if the test was routine, despite the low incidence of GBS infection in neonates. For similar reasons they were opposed to the universal administration of prophylactic antibiotics. The practical problems associated with testing were mainly the time it took to get the results, the availability of staff to use the current test equipment and interpret the results and the availability of the equipment itself. If rapid testing was shown to be accurate and is introduced into routine care, they would see it as part of their professional responsibilities. They could also see it having a role in a mixed methods strategy alongside screening in late pregnancy and professional risk assessment.

Strengths of the study

This is the first large-scale study to be published on rapid testing for GBS during labour that has sought the views of the women being tested themselves. The participants who agreed to take part actually had experience of the test procedure rather than being asked to imagine what the experience would be like. A range of data was collected on and from the women and this allowed the analysis of influences of demographic and other variables on satisfaction with and acceptability of different aspects of testing to be carried out. Rather than asking generic questions about satisfaction and acceptability, various aspects of the process were explored, as well as views on the use of testing during labour as part of routine care. The study also included an analysis of those women who declined to take part in the study and incorporated the views of midwives who had worked on the study.

Limitations of the study

The main limitation of this study is that it was not a treatment trial and so women only experienced the test procedure. No woman was treated on the basis of the test result and the participants may not have realised what treatment would have involved. Other

studies have shown that high false-positives and missed cases affect the acceptability of screening procedures.¹⁰⁵

Alternative methods of preventing GBS transmission were not discussed with the women involved in the study so they could not give their views on their preferences for screening in late pregnancy, the administration of universal prophylactic antibiotics or the possibility of a vaccination being developed to be taken during pregnancy. A small qualitative study⁷⁷ found that women in Canada did not feel that the low risk associated with GBS warranted the use of antibiotics but were also wary of taking a vaccine during pregnancy, should this become available. Only those who had direct experience of delivering a baby with GBS infection endorsed the vaccine.

Similarly, details of treatment with intravenous antibiotics during labour were not discussed with all women. Only those who were being given antibiotics anyway would have been made aware of what this involved. Lack of knowledge of the treatment regime may have influenced the views of women on satisfaction with information and acceptability of rapid testing in routine care.

The study involved women opting in rather than opting out. Many women who were approached did not agree to take part. This leads to inevitable biases in the sample. Women from South Asian ethnic origins were under-represented in the sample of those swabbed, for various reasons, including language barriers. As this group was generally more negative about rapid testing than white British and Irish and black Caribbean women, the overall acceptability of the test is likely to be overestimated. Women of any ethnicity who objected strongly to the swabs also did not take part. Again this may have led to an overestimation of the acceptability of the procedure.

As this study was not a treatment trial, midwives reported that they were less concerned about ensuring that all women who could be were swabbed. Therefore, a woman being in pain, being very young or not seeming to have a good level of English were all given as reasons by the midwives for not raising participation in the study. There is no way of knowing what effect missing out these possible participants had on the estimations of women's evaluations of the test.

Findings in the light of limitations

Women's views on rapid testing in practice have to be interpreted in the light of the fact that their deliveries were not affected by the study. They only experienced the sampling procedure. However, those who underwent this procedure were positive and their views on the introduction of testing as part of routine care are valuable.

A qualitative study of women's attitudes to GBS and screening⁷⁶ showed that most women knew very little about GBS and those who underwent screening did so because it was part of routine care and perceived to be better for the baby. The Canadian study cited above showed that how positive women were towards treatment for GBS was dependent on their experience and level of knowledge.⁷⁷ In this study those for whom GBS was salient, through their own experience of it, would be expected to have more knowledge. This group was more suspicious that the test could be carried out properly in practice as well as less confident that they would be free to make treatment choices, but, interestingly, this group also reported that they felt that the test was more important than the group for whom GBS was not salient.

It is important that those who have risk factors for GBS transmission find any screening procedure acceptable. Studies of HIV screening have shown that women at risk may be less likely to be tested, although this may be because of the impact of the results on women themselves and lifestyle characteristics, which influence the uptake of maternity care generally. In this study those in the higher risk category did not differ in their views of testing from those in the lowest risk category, except that they believed that the rapid test was more important for them to have. What is not known is how many of the women who declined to take part in the study initially were in the higher risk categories.

However, if those falling into the higher risk categories are likely to receive treatment regardless of their GBS status being known, which is essentially what current standard care in the participating hospitals offers, it is more important that those not falling into one of the higher risk categories find screening acceptable. These would be the people who would be missed under this regime. As we have seen, there is no evidence that the lower risk group finds the test less acceptable.

If testing for and treating GBS is to be introduced successfully, it is important that midwives are positive about it in their roles both in the community and in the delivery suite. The focus groups consisted of midwives with wide experience including those with current or recent experience of working in the community. Generally the midwives were positive, and this is further supported by the recruitment rates to the study. However, they did emphasise the practical problems of introducing the system, especially as it is now configured. They also had some doubts that introducing routine screening during labour would be cost-effective or justifiable given the incidence of GBS infection in neonates.

Ramifications for the economic model

The midwives in this study were opposed to the overuse of antibiotics, and felt that the women they saw would endorse this view. Therefore any strategy that involved the widespread unnecessary use of antibiotics would be unlikely to be successful in practice. The midwives also reported that they were able to take samples and process them because the timings were not important: the swabs could be taken and then analysed at a later time. If this was to become routine care, then ensuring that the test was carried out in a timely fashion and the results reported back to the midwife would be crucial. Midwives would expect to carry out the tests themselves, as they have professional responsibility for the mother, increasing the demands on their time rather than the time of midwifery assistants. They could not see the current diagnostic procedure, i.e. having the testing hardware in a separate room, fitting into their normal practice. They favoured testing hardware that would be available by the bedside for ease of use and confidentiality.

Both the women tested and the midwives found rectal testing more embarrassing and unpleasant than vaginal testing. If more rectal swabs are missed as a result of this, then this may impact on how many cases are missed.

Recommendations for practice

There are some features of current care that could be improved and some recommendations about the introduction of rapid testing if the technology continues to develop. The first is that midwives need to be better informed about GBS and the

treatment for it; this will enable them to better inform women affected and better follow current guidelines.

For women to be able to make informed choices about their care, information needs to be given about GBS closer to the time at which testing and treatment can be carried out effectively. Giving information early in pregnancy, when women have many decisions to make, means that it is likely to be forgotten. Routine information giving later in pregnancy would be more beneficial.

In general, women from South Asian groups and younger women were less positive about the results of the test being used as the basis for treatment in routine care. They would prefer to be treated on the basis of the judgment of their doctors or midwives. This is essentially the status quo. This may reflect a greater confidence in professionals in these groups; however, it may also be linked to the acceptability of the test procedure and a lack of confidence that the test would be carried out properly at that stage. Testing during pregnancy may be more acceptable to these groups for these reasons, but further education on the accuracy of the test would be necessary in any case. If testing for GBS during the late stages of pregnancy is introduced with or without testing during labour, processes for communication of results need to be improved.

If testing during labour does become available, careful consideration needs to be made of the testing procedure so that it fits into midwifery practice. Staffing concerns also need to be overcome.

Recommendation for research

This study suggests that there is enough support for GBS testing during labour for the tests to be developed further. The procedure for collecting samples is largely acceptable to women and midwives although vaginal swabs were preferred by both groups to rectal swabs. To be suitable for routine care the devices need to be not only accurate but also easy to use and genuinely rapid. More research is needed on the views of midwives on routine testing during labour.

Many women did not take part in this study because of language barriers. It is important that groups of women are not disadvantaged through non-inclusion in research. In future studies

midwives could be encouraged to assess the communication skills of potential participants and other barriers to participation more formally.

More research is also needed on the views of pregnant women and mothers who would be affected by GBS screening during pregnancy and labour. Compared with other areas of antenatal and perinatal screening, very little research has been undertaken on women's beliefs about GBS and their own risks, and whether they would

welcome testing during pregnancy, including home testing, testing during labour or indeed universal prophylactic treatment.

More work also needs to be carried out on the development of the intervention, including not only the development of the equipment but also the procedure, and such work needs to incorporate the views of the women and health professionals involved.

Chapter 4

Economic evaluation

Introduction

The economic evaluation component of the research addressed the decision problem of what is the most cost-effective strategy for the antenatal screening and management of EOGBS disease.

In considering this question a total of 10 strategies have been researched and are compared:

1. routine untargeted IAP to all (treat all)
2. no screening and no antibiotic prophylaxis (do nothing)
3. culture of vaginal and rectal swabs taken at 35–37 weeks' gestation
4. rapid testing during labour using PCR [rapid test 1 (PCR)]
5. rapid testing during labour using 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) – only have rapid test 1 if mother has risk factors (risk factors positive, PCR positive)
8. risk factors and rapid test 1 (PCR) – only have rapid test 1 if mother has no risk factors (risk factors negative, PCR positive)
9. risk factors and rapid test 2 (OIA) – only have rapid test 2 if mother has risk factors (risk factors positive, OIA positive)
10. risk factors and rapid test 2 (OIA) – only have rapid test 2 if mother has no risk factors (risk factors negative, OIA positive).

The justification for these strategies has been broadly explained in Chapter 1 (see The evidence base for screening strategies) but some additional explanation is required for some of the strategies. Strategies 1 and 2 depict theoretical combinations that have no direct clinical relevance but which are nonetheless important for a complete understanding of the relationship between benefits and costs. For strategies 7 and 9 the addition of the rapid test to confirm the result of screening based on risk factors can help to avoid false-positive results. Strategies 8 and 10 are justified by the fact that the risk factor-based approach is crude and so carrying out a PCR or OIA rapid test might prove an important strategy in minimising the number

of false-negative results, given that the costs associated with EOGBS disease are so great.

In this chapter the economic evaluation of the alternative strategies for detecting and treating GBS is described. The construction of the model, the cost data collection, the clinical data synthesis and the analysis are described in detail.

Methods

The economic evaluation is carried out from the perspective of the NHS in the UK and the primary outcome is presented in terms of the cost per case of EOGBS-associated infant death avoided. The results are also presented in terms of the cost per case of EOGBS disease avoided. Resource use data associated with risk factor-based screening, culture-based screening and carrying out the PCR and OIA rapid tests were collected prospectively alongside the study. The resource use and costs associated with the culture test based on a swab taken during labour, which was used as the gold standard in the analysis of accuracy, were used as a proxy for the costs associated with a culture test at 35 weeks' gestation, which is included in the economic analysis. The resource use was assessed only in the Birmingham centre, chosen because it was the largest centre in the study in terms of the numbers of deliveries and consenting women. It was also chosen for convenience. However, cross-checks made as part of the study by the research midwife confirmed that practice and resource use in the different centres did not differ significantly. Costs attached to resource use were taken from standard sources such as Curtis and Netten,¹²¹ UK Healthcare Related Group (HRG) cost data (DoH), NHS prices^{129,130} and Birmingham Women's Hospital.

The primary clinical data used in the analysis include the results of testing based on the PCR and OIA rapid tests, the accuracy of these tests when compared with the gold standard of culture in terms of sensitivity and specificity (*Table 52*, Appendix 6), and the actual outcomes of women and their babies as a result of risk factor-based screening only; these data were collected

prospectively from the study. The accuracy of culture at 35 weeks was based on an estimate from the literature.⁶⁹ Other data required for the analysis, such as the population prevalence of EOGBS disease and UK rates of infant mortality, were sourced from the literature and other secondary sources.

Model structure

In this primary study no action in terms of treatment is taken on the basis of the PCR or OIA rapid test that is carried out on consenting women because it is carried out in addition to risk factor-based screening, which they should receive as part of current practice. The only action that is taken is on the basis of the risk factor-based screening. Thus there is no comparator in terms of outcomes for women whose rapid test results are contrary to those predicted by risk factor-based screening. Hence, a model is required to carry out the analysis. A decision tree was considered to be the most appropriate model for this study, given the short-term nature of the decision problem.¹²² The model was constructed in DATA TreeAge (TreeAge Software, 2005; Williamstown, MA, USA).

Figure 7 presents an overview of the decision tree and the 10 policy alternatives that have been modelled. Separate subtrees are presented for the strategies listed in Figure 7. For each strategy in turn the model considers the number of EOGBS-associated deaths, the number of EOGBS disease cases and the associated costs. Space constraints do not allow the entire tree to be presented but subtrees 1 (Figure 8) and 4 (Figure 9) are presented as an illustration and the remainder of the subtrees are presented in Appendix 7.

Figure 8 (subtree 1) represents the ‘routine untargeted IAP to all’ option. It presents the possible paths that might be followed under such a regimen (i.e. no systematic testing but untargeted treatment with antibiotics of women in labour). The assumption here is that all women would be given antibiotics intravenously as soon as they are admitted in labour. The analysis assumes that clindamycin and penicillin are the antibiotics offered in line with current practice at Birmingham Women’s Hospital and as per the Green-top Guideline of RCOG.⁶¹

Subtree 2 (Appendix 7, Figure 20) represents the ‘do nothing’ strategy. Here, women are not screened for GBS and are also not given antibiotics, regardless of risk factors. In subtree 3 (Appendix 7, Figure 21) the use of a culture test at 35–37 weeks’ gestation by culture of vaginal and rectal swabs is introduced. This strategy is based on the US Centers for Disease Control and Prevention recommendations that all pregnant women undergo bacteriological screening,¹²³ with all women testing positive for GBS then given IAP. However, because of the high risk of EOGBS disease associated with preterm birth, the assumption is made that all mothers presenting in labour before 35–37 weeks’ gestation receive IAP.

Subtree 4 (Figure 9) and subtree 5 (Appendix 7, Figure 23) present the key alternatives that the current study aimed to compare, namely the rapid tests, PCR and OIA. Figure 9 presents the subtree for PCR; the subtree for OIA is exactly the same and is presented in Appendix 7, Figure 23. For the strategy of the rapid test based on PCR or OIA, all women presenting in labour are tested for GBS and those who test positive are treated with antibiotics.

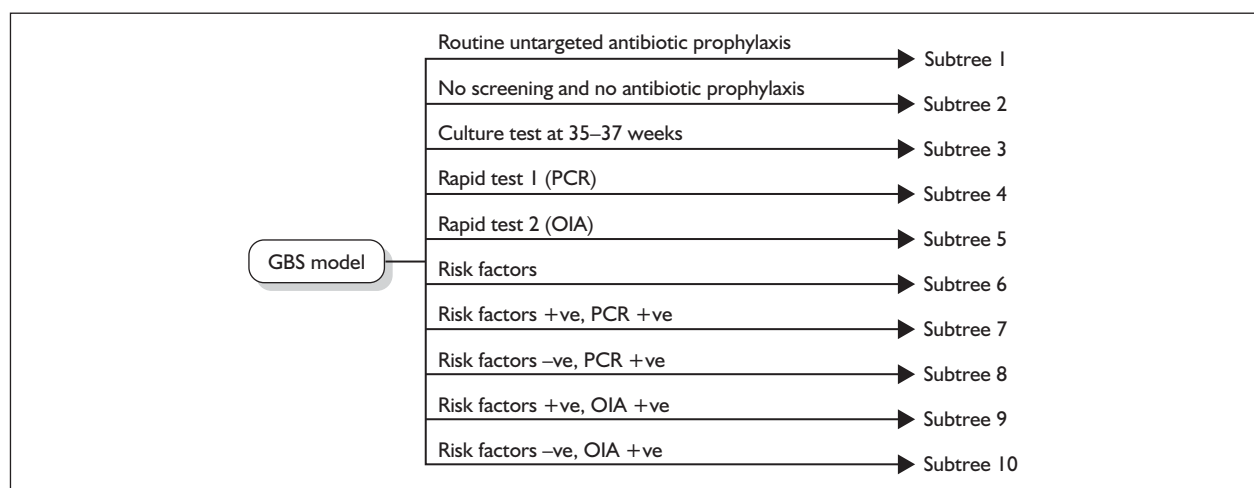


FIGURE 7 Model structure. OIA, optical immunoassay; PCR, polymerase chain reaction.

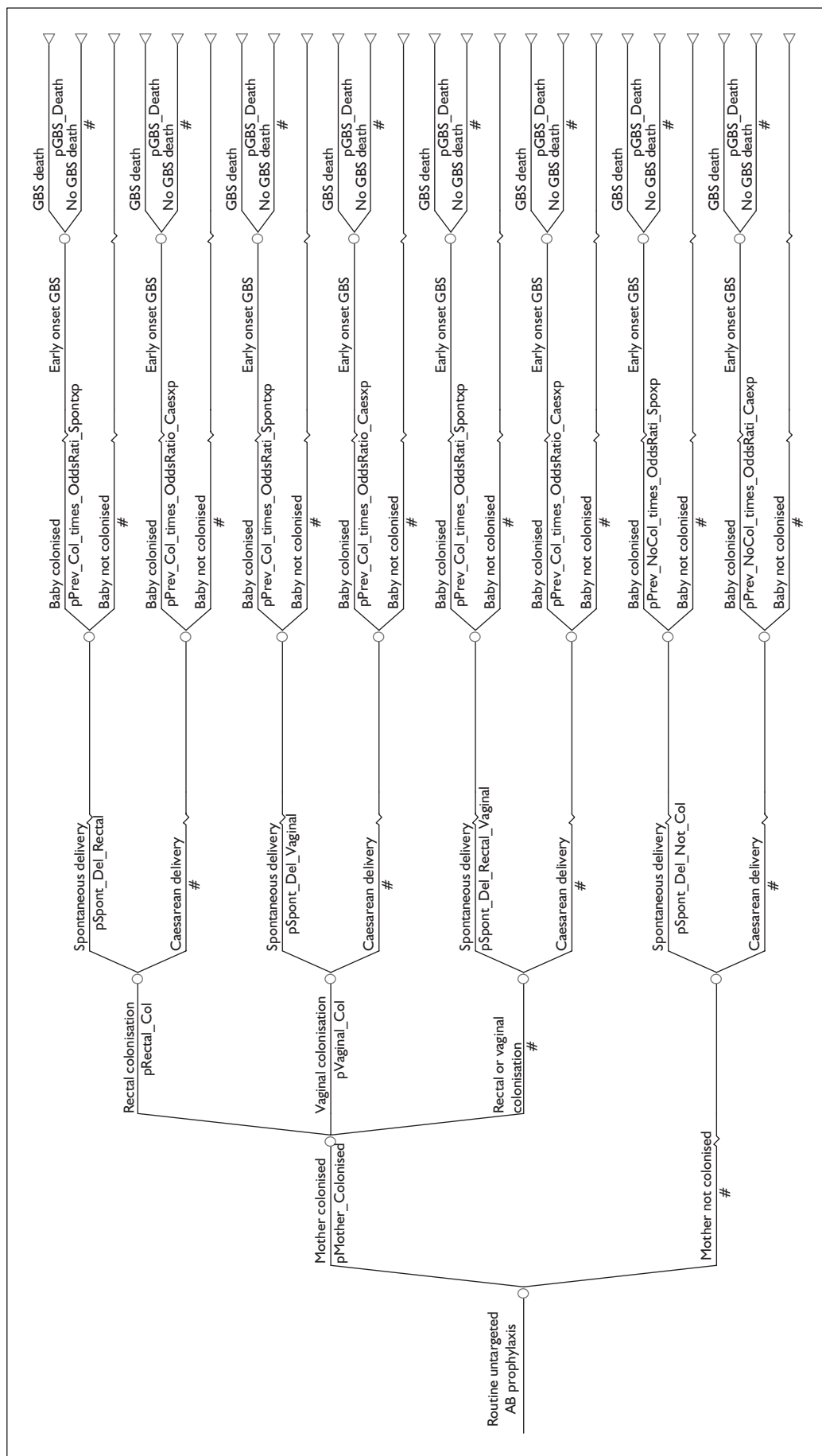


FIGURE 8 Subtree 1. AB, antibiotic.

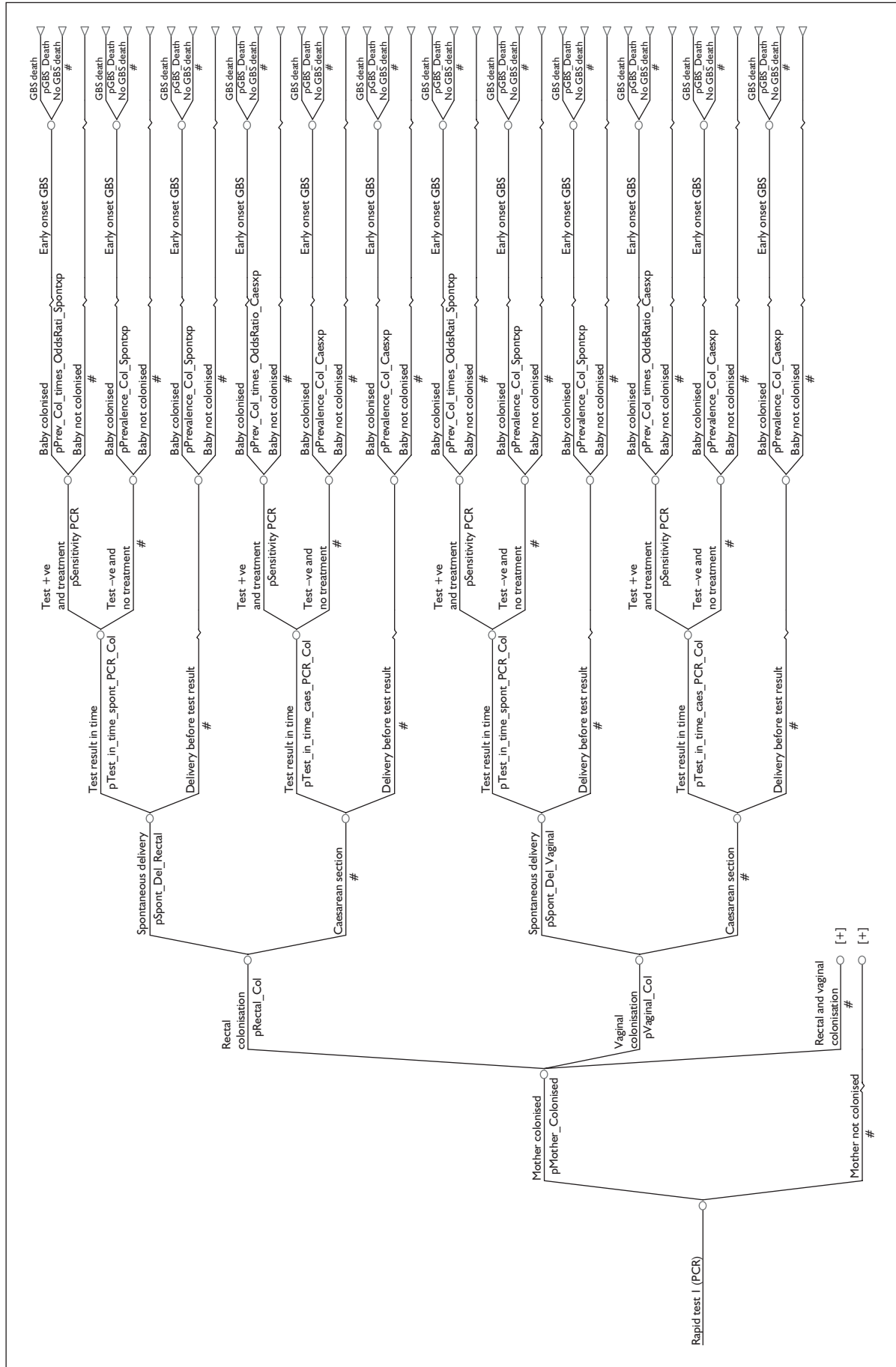


FIGURE 9 (a) Subtree 4.

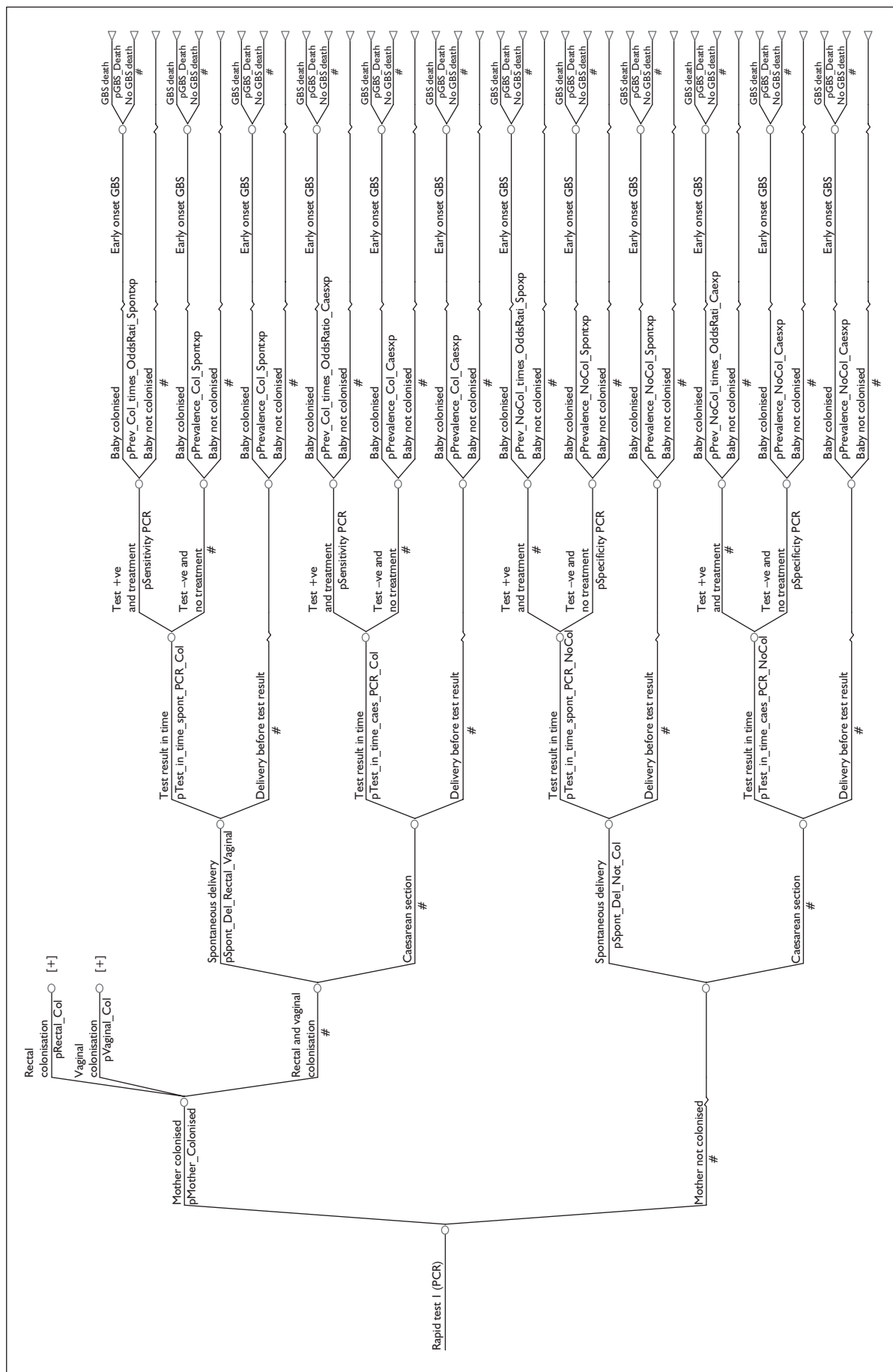


FIGURE 9 (b) Subtree 4 (continued).

In subtree 6 (Appendix 7, *Figure 24*), women who have at least one of five risk factors are treated with antibiotics. The five risk factors are previous EOGBS-affected baby, preterm labour, GBS bacteriuria detected during the current pregnancy, PROM and fever in labour.

Subtrees 7–10, presented in Appendix 7, outline the strategies that are a combination of the risk factors and rapid tests. In *Figure 25* women who possess one or more of the five risk factors are further tested for GBS using the PCR test and are only treated if the test result is positive. *Figure 27* presents a similar strategy but with the exception that the rapid test used in this case is the OIA. In *Figure 26* women who possess one or more of the five risk factors are treated with antibiotics whereas 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. In *Figure 28* the strategy is repeated but for the rapid test based on OIA.

Model data

For each strategy in the model the underlying maternal colonisation rate is required. The colonisation rates are presented in *Table 18*. The parameter ‘overall maternal colonisation’ represents the overall maternal colonisation rate expressed as a probability ($p = 0.2128$). This implies that 0.7872 is the underlying probability of overall maternal non-colonisation. Maternal colonisation was further characterised by the site of colonisation (i.e. rectal only, vaginal only and both rectal and vaginal combined). Again the parameters ‘rectal only’ and ‘vaginal only’ represent probabilities associated with rectal only and vaginal only colonisation respectively. Because probabilities need to sum to one, a formula ensures that the probability for both rectal and vaginal colonisation is the difference, defined as $[1 - (\text{rectal only} + \text{vaginal only})]$. There is evidence to suggest that the risk of GBS transmission from mother to baby will differ by type of delivery.¹²⁴ Therefore, in the model, vaginal delivery was distinguished from Caesarean delivery.

The overall neonatal colonisation rate (weighted by mode of delivery and maternal colonisation), which was estimated in the current study to be 0.0921, is presented in *Table 19*. The prevalence of EOGBS disease given neonatal colonisation has been estimated elsewhere to be 0.027.⁶⁹ However, the product of this estimate and the overall neonatal colonisation rate should result in the observed incidence of EOGBS disease in the

absence of systematic screening or widespread IAP in the entire population, which is approximately 0.5 per 1000.⁶¹ As the overall neonatal colonisation rate was calculated from the new empirical data estimated by the current study it is considered more accurate than estimates from other sources. Thus, it was necessary to calibrate the prevalence of EOGBS disease, given neonatal colonisation, to obtain the ‘correct’ value of the population incidence of EOGBS disease in the absence of systematic screening or widespread IAP. This resulted in a value of 0.00518 being obtained for the prevalence of EOGBS disease given neonatal colonisation.

Table 19 also shows the neonatal colonisation prevalence, calculated from the data in the current study. The details of the calculation are given in Appendix 6. The treatment effect of maternal antibiotics associated with a baby developing EOGBS disease, given maternal colonisation, was obtained from other sources.⁶⁹ When a mother received intravenous antibiotics, the OR for the effect of antibiotic therapy on EOGBS disease was used together with the prevalence of neonatal EOGBS disease in the calculation of the outcome. When no antibiotics were given to the mother, the prevalence alone was used. The terminal nodes indicate the main outcomes, which are EOGBS-related deaths avoided and cases of EOGBS disease avoided.

Test accuracy and effectiveness inputs

The overall mother colonisation rates were obtained from the results of the enriched culture tests used on all women who presented at labour in this study. These are shown in *Table 20*. These culture tests were also the source of information for the site of maternal colonisation, shown in *Table 18*.

The majority of the accuracy and effectiveness data estimates used in the model were collated from the current GBS study and supplemented where necessary using published sources, as illustrated in *Table 20*.

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. For a PCR test it was assumed that the test results would be ready before the woman delivered if the time period between the swab being taken and delivery was at least 80 minutes. This time was determined through a ‘time and motion study’ conducted as part of this project. The full details of the time and motion study, which estimated the time and costs

TABLE 18 Maternal colonisation rates

Parameter	Value (95% CI)	Source
Overall maternal colonisation	0.2128 (0.1913–0.2343)	GBS study
Site of colonisation		
Rectal only	0.2746 (0.2237–0.3255)	GBS study
Vaginal only	0.0949 (0.0615–0.1283)	GBS study
Both rectal and vaginal	0.6305 (0.5754–0.6856)	GBS study
Site of colonisation by type of delivery		
Rectal only and vaginal delivery	0.7778 (0.6873–0.8683)	GBS study
Rectal only and Caesarean delivery	0.2222 (0.1317–0.3127)	GBS study
Vaginal only and vaginal delivery	0.7500 (0.5896–0.9104)	GBS study
Vaginal only and Caesarean delivery	0.2500 (0.8960–0.4104)	GBS study
Both rectal and vaginal and vaginal delivery	0.7043 (0.6387–0.7699)	GBS study
Both rectal and vaginal and Caesarean delivery	0.2957 (0.2301–0.3613)	GBS study
No maternal colonisation		
Overall	0.7872 (0.7657–0.8087)	GBS study
Vaginal delivery	0.7972 (0.7733–0.8211)	GBS study
Caesarean delivery	0.2028 (0.1789–0.2267)	GBS study

TABLE 19 Neonatal prevalence and treatment effect of antibiotics

Parameter	Value (95% CI)	Source
Prevalence of neonatal colonisation		
Maternal colonisation and vaginal delivery	0.4630 (0.3942–0.5318)	GBS study
Maternal colonisation and Caesarean delivery	0.2280 (0.1312–0.3250)	GBS study
No maternal colonisation and vaginal delivery	0.0099 (0.0031–0.0167)	GBS study
No maternal colonisation and Caesarean delivery	0.0051 (–0.0048 to 0.015)	GBS study
Overall neonatal colonisation (weighted average)	0.0921 (0.0521–0.1319)	GBS study
Incidence of EOGBS disease given neonatal colonisation	0.00518 (0.00375–0.00661)	Calibrated (0.000477/0.0921)
Incidence of EOGBS disease in the absence of systematic screening or widespread IAP	~0.0005 (0.5/1000 live births)	RCOG 2003 ⁶¹
Treatment effect of IAP		
OR for the effect of maternal antibiotics on EOGBS disease given maternal colonisation – Cochrane estimate ^a	0.17 (0.07–0.39)	Smaill 2003 ³⁸
OR for the effect of maternal antibiotics on EOGBS disease given maternal colonisation – Colbourn <i>et al.</i> ⁶⁹ estimate ^b	0.028 (0.0015–0.12)	Colbourn <i>et al.</i> 2007 ⁶⁹

IAP, intravenous antibiotic prophylaxis; OR, odds ratio; RCOG, Royal College of Obstetrics and Gynaecology.
a Calculated using Peto one-step OR method, which produces the least biased estimates for rare events.¹²⁵
b Used in sensitivity analysis.

TABLE 20 Sensitivity and specificity of rapid tests

Parameter	Value (95% CI)	Source
PCR test		
<i>Overall</i>		
Sensitivity	0.5836 (0.5249–0.6407)	GBS study
Specificity	0.9216 (0.8978–0.9414)	GBS study
<i>Given presence of risk factors</i>		
Sensitivity	0.697 (0.590–0.790)	GBS study
Specificity	0.905 (0.857–0.941)	GBS study
<i>Given absence of risk factors</i>		
Sensitivity	0.534 (0.463–0.604)	GBS study
Specificity	0.926 (0.906–0.942)	GBS study
OIA test		
<i>Overall</i>		
Sensitivity	0.3478 (0.2893–0.4100)	GBS study
Specificity	0.9178 (0.892–0.9393)	GBS study
<i>Given presence of risk factors</i>		
Sensitivity	0.474 (0.360–0.591)	GBS study
Specificity	0.913 (0.862–0.949)	GBS study
<i>Given absence of risk factors</i>		
Sensitivity	0.291 (0.225–0.365)	GBS study
Specificity	0.919 (0.897–0.938)	GBS study
Culture test		
Sensitivity	0.7580 (0.4720–0.9150)	Colbourn et al. 2007 ⁶⁹
Specificity	0.9470 (0.8850–0.9850)	Colbourn et al. 2007 ⁶⁹
Risk factors		
Sensitivity	0.3131	GBS study
Specificity	0.7979	GBS study

OIA, optical immunoassay; PCR, polymerase chain reaction.

associated with the rapid test, are presented in Appendix 6. The corresponding time for an OIA test was 37 minutes. These results are shown in Tables 40–42.

The data presented in Table 20 are derived from rapid tests of vaginal swabs compared with enriched culture of combined vaginal and rectal swabs as the reference standard.

The infant mortality rate for the population and the infant mortality rate in infants with EOGBS disease are presented in Table 21. From these figures the additional mortality due to EOGBS disease alone is estimated to be 0.0746.

Costs

Table 22 presents a summary of all of the costs used in the model. These were obtained from various sources including Birmingham Women's Hospital, Curtis and Netten¹²¹ and NHS prices.^{128,129} More detailed information on the costing methods used is presented in Appendix 6, Table 43. All costs are reported in UK pounds and have a common price year of 2005/6.

Analysis

Two sets of model-based analyses have been undertaken:

TABLE 21 Infant mortality rates

Parameter	Value	Source
Mortality rates		
(a) Population infant mortality rate	0.0054	Office for National Statistics 2005 ¹²⁶
(b) Mortality rate in infants with EOGBS disease ^a	0.0800	Weisner <i>et al.</i> 2004 ¹²⁷
(c) Additional mortality due to EOGBS disease in EOGBS disease population ^b	0.0746	(b) – (a)
(d) Additional mortality due to EOGBS disease in entire population	0.0000373	(c) × incidence of EOGBS disease in the absence of systematic screening or widespread IAP (0.0005 from <i>Table 19</i>)
EOGBS, early-onset group B streptococcus; IAP, intravenous antibiotic prophylaxis.		
a Infant mortality can be the result of EOGBS disease or other causes.		
b Infant mortality due to EOGBS disease alone.		

TABLE 22 Summary costs per patient for group B streptococcus (GBS)

Cost item	Cost (£)	Source
Tests		
PCR (vaginal or rectal)	29.95	Appendix 6, <i>Table 43</i>
OIA (vaginal or rectal)	16.09	Appendix 6, <i>Table 43</i>
Culture (mother)	10.63	Appendix 6, <i>Table 44</i>
Antibiotics		
Penicillin	14.49	Appendix 6, <i>Table 43</i>
Clindamycin	12.17	Appendix 6, <i>Table 43</i>
Cost of delivery		
Normal delivery	891.00	Appendix 6, <i>Table 43</i>
Caesarean delivery	1643.00	Appendix 6, <i>Table 43</i>
Cost of disease		
Mother (cost of treatment)	14.28	Appendix 6, <i>Table 43</i>
Baby		
EOGBS – death	1537.91	Appendix 6, <i>Table 43</i>
EOGBS – no death	534.25	Appendix 6, <i>Table 43</i>
Cost of identifying risk factors		
Weighted total	2.96	Appendix 6, <i>Table 43</i>
EOGBS, early-onset group B streptococcus; OIA, optical immunoassay; PCR, polymerase chain reaction.		

- analysis 1, in which all 10 alternative strategies for identifying and treating women at risk of GBS are considered
- analysis 2, a restricted analysis that considers only nine strategies – routine untargeted IAP is excluded.

Analysis 2 was considered necessary because a strategy of providing routine antibiotics to all women may not be acceptable to women or their midwives, as discussed in Chapter 3.

The base case for each analysis is carried out using the accuracy results based on the vaginal swab compared with a combined vaginal and rectal enriched culture reference standard; the Cochrane OR for the effect of maternal antibiotics therapy on EOGBS disease given maternal colonisation; and an outcome of EOGBS-associated infant deaths avoided/cases of EOGBS disease avoided.

The results, in terms of the incremental cost-effectiveness ratios (ICERs), are expressed as the additional cost for each EOGBS-associated infant death avoided. The analysis also reports an ICER in terms of the cost for each additional infant case of EOGBS disease avoided. There are no available primary studies that have measured the quality of life in children who have experienced and survived EOGBS disease. One study⁶⁹ has produced estimates for quality of life decrements, based on published estimated disability impairment associated with childhood illnesses such as meningitis, and applied these to the quality of life associated with EOGBS disease. As the estimates are based on data from just one published study, and given the difficulty of accurately representing the quality of life associated with disability in children, the robustness of such estimates and their application to the decision process must be viewed with caution.

Studies presenting results in ‘natural units’ such as cost per case of death or disease avoided can be compared amongst themselves but are less useful for decision-making because there are no agreed thresholds for cost-effectiveness measured in natural units such as these. Decision-makers in the UK NHS, such as the National Institute for Health and Clinical Excellence (NICE), use an ICER for decision-making, with a standard unit of benefit, the quality-adjusted life-year (QALY). To allow some comparison with the criteria applied by NICE, albeit using ball-park estimates, a crude conversion has been applied from EOGBS deaths avoided to QALYs (see Appendix 6 for details).

For ICERs that fall below the threshold of £20,000 per QALY, the intervention is likely to be accepted on cost-effectiveness grounds. NICE guidance¹³⁰ states that:

Above a most plausible ICER of £20,000/QALY, judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make more explicit reference to factors including: the degree of uncertainty around the calculation of the ICERs ...

The cost-effectiveness analyses have been undertaken using both deterministic and probabilistic approaches. Under the former there is no randomness in the model calculations and during each calculation; each model parameter uses its specified point value. As there is no predetermined acceptable threshold for ICERs of interventions associated with this disease, we present the ICERs ranked in terms of their relative cost-effectiveness compared with a ‘do nothing’ strategy.

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was carried out for the base-case analysis only, for analyses 1 and 2, to explore the effects on the ICERs of the uncertainty in the model input data.

In probabilistic analysis, each model parameter is assigned a distribution reflecting the amount and pattern of its variation, and cost-effectiveness results are calculated by simultaneously selecting random values from each distribution. The process is repeated many times in a Monte Carlo simulation of the model to give an indication of how variation in the model parameters leads to variation in the ICERs for a given combination of a test and treatment pairing. In total, 2000 replications were carried out. This number is arbitrary but typical standard practice. The appropriate distribution for the data on test accuracy (sensitivity and specificity) is either a beta or normal distribution depending on the statistical characteristics of the parameters. The appropriate distribution for data on intervention effectiveness is a beta distribution. These are standard distributions for these data and are deemed to be appropriate in this case.

Unit cost uncertainty is excluded from the probabilistic analysis here because any variations that might exist for unit costs are of a different

nature from the data-driven uncertainty in the patient flow parameters.

Deterministic sensitivity analysis

The following one-way deterministic sensitivity analyses were conducted.

Changing the cost associated with EOGBS death

In the base case the cost associated with EOGBS-associated death was estimated to be £1538 based on data from Colbourn *et al.*⁶⁹ In the sensitivity analysis, in both analyses, we investigated the effect on the ICER of reducing this cost to £500 and increasing it to £2000 and £3000. This range of costs was arbitrarily chosen to explore the effect of an extreme change in costs on the results.

Changing the cost associated with the culture test at 35–37 weeks

The cost associated with the culture test at 35–37 weeks' gestation was based on estimates of the resources used in performing the reference standard during the study and is presented in Appendix 6, *Table 43*. However, this estimated cost is unlikely to reflect the true cost of culture if the test becomes part of normal practice. In this situation women would have a swab taken during an antenatal appointment and, for the majority of women, this might not be in a hospital with the facilities to carry out such a test. Thus, some transportation costs associated with transferring the samples from a community antenatal clinic, for instance, to the laboratory for culture are likely to exist. In the sensitivity analysis we changed the estimated cost associated with culture to see if it had any effect on the decision.

Changing the estimated effect of IAP on EOGBS disease and death given maternal colonisation

In the base case the OR used for the effect of treatment with IAP in preventing EOGBS disease given maternal colonisation was 0.17 (95% CI 0.07–0.39), based on evidence from a Cochrane review.⁴³ In the sensitivity analysis the OR of Colbourn *et al.*⁶⁹ was used, which was much lower at 0.028 (95% CI 0.0015–0.12).

Threshold analysis for the cost of the rapid PCR test (based on vaginal swabs only)

In the base case the sensitivity and specificity of the rapid PCR test, based on using only a vaginal swab, was 0.58 and 0.92 respectively. The current

cost is £29.95. In the sensitivity analysis we assessed how low the cost of the rapid test needs to be, given its current sensitivity and specificity, for it to be the most attractive strategy in terms of cost-effectiveness.

Threshold analysis for the cost of the rapid PCR test (based on vaginal and rectal swab combined)

The sensitivity analysis defined above was repeated using the accuracy results of the rectal and vaginal swabs combined for the rapid PCR test, which has an estimated sensitivity and specificity of 0.84 and 0.87 respectively.

Removing the assumption that all women who deliver before the screening test, based on culture at 35–37 weeks, are treated with IAP

There is an established association between preterm birth and the incidence of maternal GBS colonisation.¹² In the baseline model, it was assumed that all women who deliver before 35–37 weeks' gestation, who would not have received the screening test based on culture, receive IAP. In the sensitivity analysis this assumption was removed for analysis 2 only, as it is unlikely to affect the results of the model that includes the strategy of untargeted antibiotics to all.

Threshold analysis for the cost of antibiotics (based on vaginal swabs only)

The average cost of antibiotics was estimated to be £14.28 in this study. In this analysis, we assessed what would happen if the cost of antibiotics was raised.

Results

Analysis 1

The results from the deterministic analyses are virtually identical to those from the probabilistic analyses 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 23*, with the strategies ordered from least costly to most costly. The cost and effectiveness of each strategy are presented incrementally to the one presented directly before it, except when a strategy presented is referred to as dominated, in which case the incremental costs and effectiveness are in comparison to the preceding strategy that is not dominated.

TABLE 23 Analysis 1 – base-case results: costs, effects and incremental cost-effectiveness ratios (ICERs) based on an outcome of cost per case of infant early-onset group B streptococcus disease avoided

Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER (£)
No screening and no IAP	1055		0.999524		
Risk factors	1061	6.12	0.999631	0.000107	57,038
Risk factors +ve, OIA +ve	1062	0.95	0.999567	-0.000064	(Dominated)
Risk factors +ve, PCR +ve	1065	4.16	0.999584	-0.000047	(Dominated)
Culture test at 35–37 weeks	1068	7.31	0.999778	0.000147	49,726
Routine IAP to all	1069	0.63	0.999877	0.000099	6414
Rapid test 2 (OIA)	1073	3.89	0.999635	-0.000242	(Dominated)
Risk factors –ve, OIA +ve	1075	5.77	0.999695	-0.000181	(Dominated)
Risk factors –ve, PCR +ve	1086	16.84	0.999742	-0.000135	(Dominated)
Rapid test 1 (PCR)	1087	18.27	0.9997	-0.000177	(Dominated)

IAP, intravenous antibiotic prophylaxis; OIA, optical immunoassay; PCR, polymerase chain reaction.

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. The average cost per woman for this strategy is £1055. Under a strategy of ‘do nothing’, 476 per million infants will develop the disease and 999,524 per million infants will not develop the disease. This is shown in *Table 23* under effectiveness of the intervention, which shows that 99.9524% of infants will not develop the disease and therefore $1 - 0.999524 = 0.000476$ or 476 per million infants will develop the disease. This means that a higher effectiveness represents a more favourable outcome. This result is an important cross-checking reference point for the model, because it confirms that, in the absence of screening for GBS, the effect of ‘do nothing’ is that 476 per million infants develop the disease, which concurs with the observed population rate, which is approximately 0.5 per 1000 women.⁶¹

The next least costly strategy is screening based solely on the presence of the risk factors. The average cost per woman for this strategy is £1061, an average of £6.12 more per woman than the ‘do nothing’ strategy. It is also more effective than the ‘do nothing’ strategy. Spending £6.12 million (£6.12 × 1,000,000) would mean that 107 cases ($0.000107 \times 1,000,000$) of EOGBS disease would be avoided. The ICER of this strategy compared with the ‘do nothing’ strategy is £57,038 per case of EOGBS disease avoided.

The next least costly strategies presented in *Table 23*, ‘risk factors positive, OIA positive’ and ‘risk

factors positive, PCR positive’, are both dominated by the strategy of risk factors alone in that both of these strategies are more expensive and less effective than a strategy of risk factors alone.

Screening based on a culture test at 35–37 weeks’ gestation is the next least costly strategy. At £1068 per woman it costs on average £7.31 more per woman than the strategy of screening based on risk factors but it is also more effective. For an additional £7.31 million (£7.31 × 1,000,000) an additional 147 cases of EOGBS disease could be avoided, compared with the strategy of screening based on risk factors. The ICER for screening based on the culture test at 35–37 weeks’ gestation compared with screening based on risk factors is £49,726 per case of EOGBS avoided.

The strategy of ‘routine untargeted IAP to all’ costs £0.63 more per woman than the strategy of culture at 35–37 weeks’ gestation but is also more effective. For an additional £0.63 million (£0.63 × 1,000,000), 99 cases ($0.000099 \times 1,000,000$) of EOGBS could be avoided. The ICER for the strategy of routine untargeted IAP to all compared with the strategy of culture at 35–37 weeks’ gestation is £6414 per case of EOGBS avoided.

The results presented in *Table 23* suggest that, if an ICER of £57,038 per additional case of EOGBS avoided is considered acceptable, then adopting a strategy of screening based on risk factors, as opposed to doing nothing, would be the preferred strategy. If this is the case, then the ICER of £49,726 per additional case of EOGBS disease

avoided to adopt the strategy of screening based on culture at 35–37 weeks' gestation would also be acceptable. Following this logic the ICER of £6414 per case of EOGBS disease avoided would also be acceptable and therefore the strategy of providing routine untargeted antibiotics to all would be the preferred strategy because there is considered to be extended dominance.

If the ICER of £57,038 per additional case of EOGBS disease avoided is not considered acceptable, the strategy of screening based on risk factors would not be adopted and other strategies would have to be considered. The strategy of routine untargeted antibiotics to all is presented incrementally in *Table 23* in a comparison with screening based on culture at 35–37 weeks' gestation. If this strategy, routine untargeted antibiotics to all, is compared with a strategy of doing nothing, as presented in *Table 24*, the ICER is £39,813 per case of EOGBS disease avoided, which is a more favourable ICER compared with the strategy of doing nothing than exists for the strategy of risk factors. It is therefore more cost-effective to move from the strategy of doing nothing to the strategy of routine untargeted IAP to all. This is shown in *Figure 10*. However, the acceptance of this strategy depends on whether or not the ICER of £39,813 per case of EOGBS disease avoided is considered acceptable.

In *Table 25* the results of analysis 1 are reported with the outcome expressed as EOGBS-associated infant deaths avoided. Under a strategy of doing nothing approximately 35 per million infants will die as a result of EOGBS and 999,964 per million infants will not die. This is shown in *Table 25* under effectiveness of the intervention, which shows that 99.9964% (0.999964 in the table) of infants will not die of the disease and therefore $1 - 0.999964 = 0.000035$ or 35 per million infants will develop the disease. This result concurs with the observed incidence of EOGBS-associated deaths in the population.¹⁸

When the outcome is EOGBS deaths avoided, the ICER for the strategy of screening based on risk factors compared with a strategy of doing nothing is £764,579 per death avoided (*Table 25*). However, under extended dominance, the ICER of £533,683 per EOGBS death avoided for the strategy of routine untargeted IAP to all compared with the strategy of doing nothing is more favourable and thus would be the preferred strategy if the ICER is deemed to be within an acceptable threshold. This is presented in *Table 26* and *Figure 11*.

If this ICER of £533,683 per EOGBS-associated death avoided is converted to a utility on the basis that a life in full health, discounted at the rate recommended by NICE of 3.5%, is worth approximately 27 discounted QALYs, the conversion (£533,683/27 QALYs) produces an ICER of £19,766 per QALY.

Analysis 2

In analysis 2, the analysis is repeated but the strategy of providing routine untargeted IAP to all is removed. Again, the results from the deterministic analyses are virtually identical to those from the probabilistic analyses and so it was considered acceptable to report deterministic results as the primary analysis.

In *Tables 27* and *28* the results are presented based on the outcome of cases of EOGBS disease avoided. In *Tables 29* and *30* the results presented are based on the outcome of deaths associated with EOGBS avoided.

The ICER for the strategy of screening based on risk factors compared with a strategy of doing nothing when the outcome is in terms of cases of disease avoided is £57,038 per case of disease avoided (*Table 27*). The ICER for the strategy of culture at 35–37 weeks' gestation compared with the strategy of risk factors is £49,726 per case of disease avoided. Under extended dominance the

TABLE 24 Analysis 1 – base-case results, without dominated options (simple or extended), based on an outcome of cost per case of infant early-onset group B streptococcus disease avoided

Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER (£)
No screening and IAP	1055		0.999524		
Routine IAP to all	1069	14.06	0.999877	0.000353	39,813

ICER, incremental cost-effectiveness ratios; IAP, intravenous antibiotic prophylaxis.

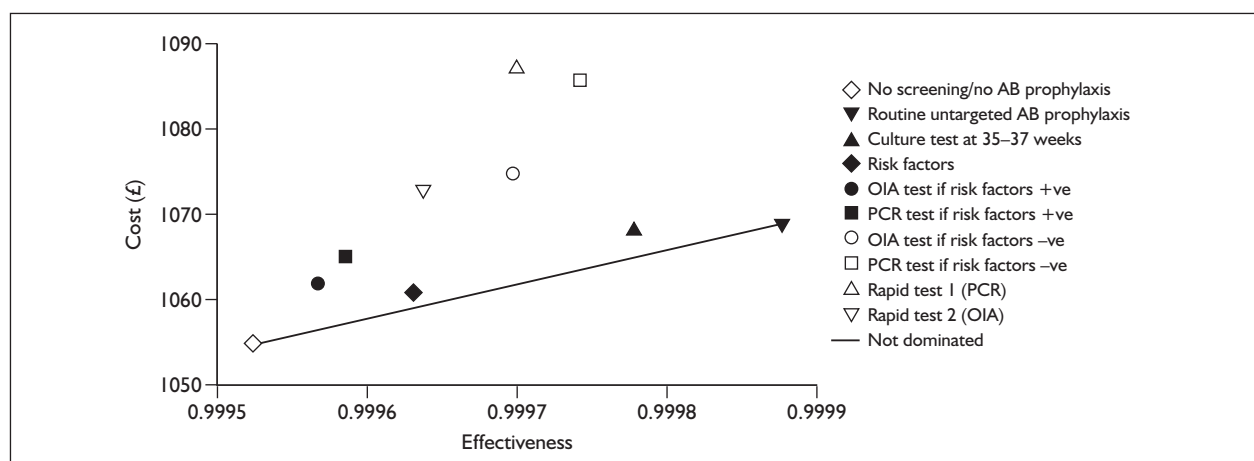


FIGURE 10 Cost-effectiveness analysis based on early-onset group B streptococcus (EOGBS) cases avoided. AB, antibiotic; OIA, optical immunoassay; PCR, polymerase chain reaction.

TABLE 25 Analysis 1 – base-case results: costs, effects and incremental cost-effectiveness ratios (ICERs) based on an outcome of cost per case of early-onset group B streptococcus-associated infant death avoided

Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER (£)
No screening and no IAP	1055		0.999964		
Risk factors	1061	6.12	0.999972	0.000008	764,579
Risk factors +ve, OIA +ve	1062	0.95	0.999968	-0.000005	(Dominated)
Risk factors +ve, PCR +ve	1065	4.16	0.999969	-0.000004	(Dominated)
Culture test at 35–37 weeks	1068	7.31	0.999982	0.000001	729,623
Routine IAP to all	1069	0.63	0.999991	0.000008	76,196
Rapid test 2 (OIA)	1073	3.89	0.999973	-0.000018	(Dominated)
Risk factors –ve, OIA +ve	1075	5.77	0.999977	-0.000014	(Dominated)
Risk factors –ve, PCR +ve	1086	16.84	0.999981	-0.000001	(Dominated)
Rapid test 1 (PCR)	1087	18.27	0.999978	-0.000013	(Dominated)

IAP, intravenous antibiotic prophylaxis; OIA, optical immunoassay; PCR, polymerase chain reaction.

TABLE 26 Analysis 1 – base-case results: costs, effects and incremental cost-effectiveness ratios (ICERs), without dominated options (simple or extended), based on an outcome of cost per case of early-onset group B streptococcus-associated infant death avoided

Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER (£)
No screening and no IAP	1055		0.999964		
Routine IAP to all	1069	14.06	0.999991	0.000026	533,683

IAP, intravenous antibiotic prophylaxis.

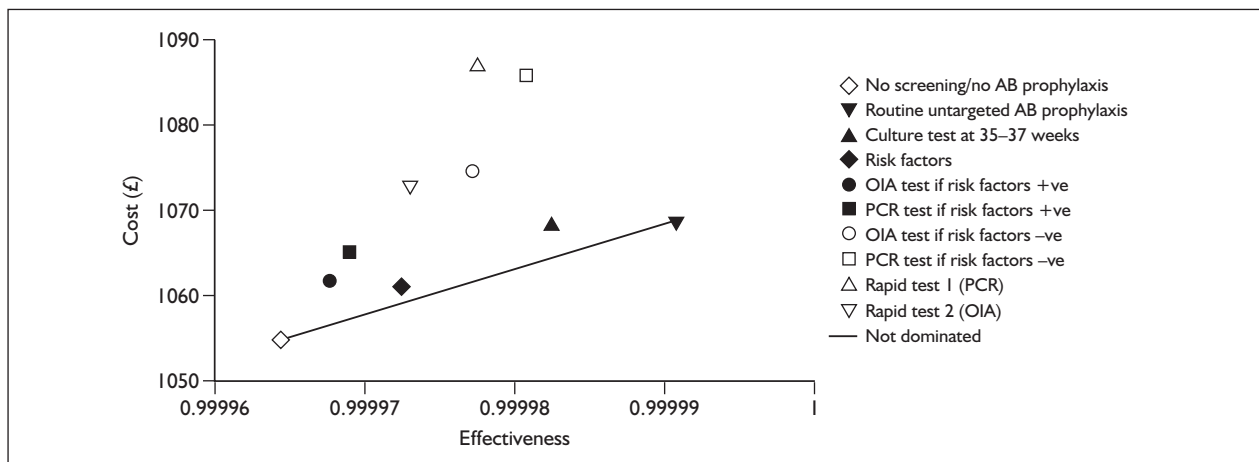


FIGURE 11 Cost-effectiveness analysis based on early-onset group B streptococcus (EOGBS) deaths avoided. AB, antibiotic; OIA, optical immunoassay; PCR, polymerase chain reaction.

TABLE 27 Analysis 2 – base-case results: costs, effects and incremental cost-effectiveness ratios (ICERs) based on an outcome of cost per case of infant early-onset group B streptococcus disease avoided

Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER (£)
No screening and no IAP	1055		0.999524		
Risk factors	1061	6.12	0.999631	0.000107	57,038
Risk factors +ve, OIA +ve	1062	0.95	0.999567	-0.000064	(Dominated)
Risk factors +ve, PCR +ve	1065	4.16	0.999584	-0.000047	(Dominated)
Culture test at 35–37 weeks	1068	7.31	0.999778	0.000147	49,726
Rapid test 2 (OIA)	1073	4.52	0.999635	-0.000143	(Dominated)
Risk factors –ve, OIA +ve	1075	6.41	0.999695	-0.000082	(Dominated)
Risk factors –ve, PCR +ve	1086	17.48	0.999742	-0.000036	(Dominated)
Rapid test 1 (PCR)	1087	18.90	0.999700	-0.000078	(Dominated)

IAP, intravenous antibiotic prophylaxis; OIA, optical immunoassay; PCR, polymerase chain reaction.

TABLE 28 Analysis 2 – base-case results: costs, effects and incremental cost-effectiveness ratios (ICERs), without dominated options (simple or extended), based on an outcome of cost per case of infant early-onset group B streptococcus disease avoided

Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER (£)
No screening and no IAP	1055		0.999524		
Culture test at 35–37 weeks	1068	13.43	0.999778	0.000254	52,810

IAP, intravenous antibiotic prophylaxis.

TABLE 29 Analysis 2 – base-case results: costs, effects and incremental cost-effectiveness ratios (ICERs) based on an outcome of cost per case of early-onset group B streptococcus-associated infant death avoided

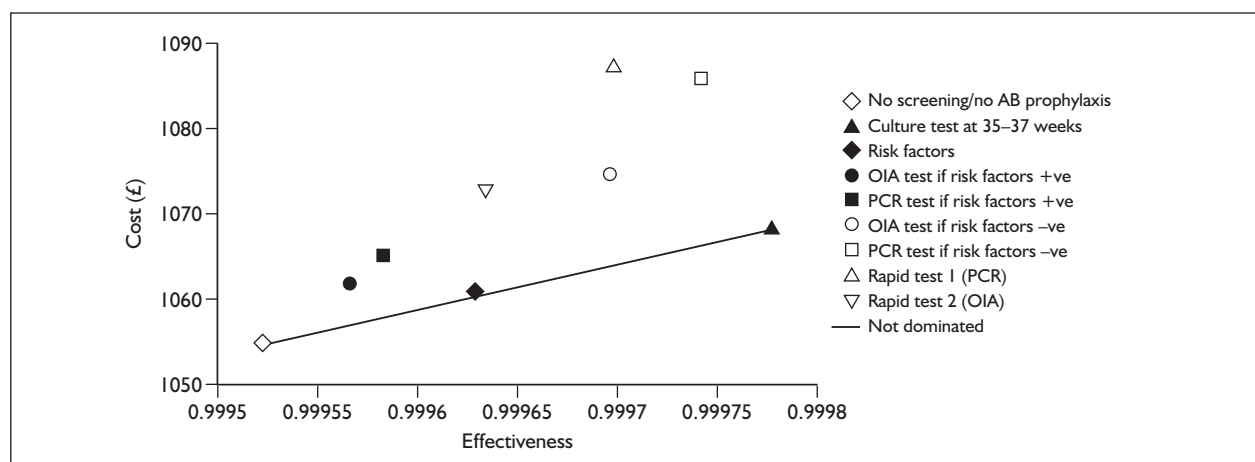
Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER (£)
No screening and no IAP	1055		0.999964		
Risk factors	1061	6.12	0.999972	0.000008	764,579
Risk factors +ve, OIA +ve	1062	0.95	0.999968	-0.000005	(Dominated)
Risk factors +ve, PCR +ve	1065	4.16	0.999969	-0.000004	(Dominated)
Culture test at 35–37 weeks	1068	7.31	0.999982	0.00001	729,623
Rapid test 2 (OIA)	1073	4.52	0.999973	-0.00001	(Dominated)
Risk factors –ve, OIA +ve	1075	6.41	0.999977	-0.000005	(Dominated)
Risk factors –ve, PCR +ve	1086	17.48	0.999981	-0.000002	(Dominated)
Rapid test 1 (PCR)	1087	18.90	0.999978	-0.000005	(Dominated)

IAP, intravenous antibiotic prophylaxis; OIA, optical immunoassay; PCR, polymerase chain reaction.

TABLE 30 Analysis 2 – base-case results: costs, effects and incremental cost-effectiveness ratios (ICERs), without dominated options (simple or extended), based on an outcome of cost per case of early-onset group B streptococcus-associated infant death avoided

Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER (£)
No screening and no IAP	105		0.999964		
Culture test at 35–37 weeks	1068	13.43	0.999982	0.000018	745,142

IAP, intravenous antibiotic prophylaxis.

**FIGURE 12** Cost-effectiveness analysis based on early-onset group B streptococcus (EOGBS) cases avoided – routine intravenous antibiotic prophylaxis excluded. AB, antibiotic; OIA, optical immunoassay; PCR, polymerase chain reaction.

ICER for the strategy of culture at 35–37 weeks' gestation compared with the strategy of doing nothing is the most favourable at £52,810 per case of disease avoided (Table 28). This result is presented diagrammatically in Figure 12. This would be the preferred strategy only if the ICER is deemed to be within an acceptable threshold.

In Table 29 the results of analysis 2 are presented with effectiveness measured in terms of deaths avoided. The ICER for the strategy of risk factors compared with a strategy of doing nothing is £764,579 per infant death avoided. The ICER for the strategy of culture test at 35–37 weeks' gestation compared with the strategy of risk factors is £729,623 per infant death avoided. Under extended dominance the comparison of the strategies of culture test at 35–37 weeks' gestation and doing nothing provides a slightly more favourable ICER of £745,142 per death avoided, compared with the comparison of the strategies of screening based on risk factors and doing nothing (£764,579) (Table 30 and Figure 13). However, this would be the preferred strategy only if the ICER of £745,142 per death avoided is deemed to be within an acceptable threshold.

If this ICER of £745,142 per EOGBS-associated death avoided is compared with the current NICE threshold and on the basis that a life in full health, discounted at the discount rate recommended by NICE of 3.5%, is worth approximately 27 discounted QALYs, the appropriate conversion (£745,142/27 QALYs) produces an ICER of £27,500 per QALY.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was carried out on the base case in terms of pairwise comparisons for the following strategies:

- routine untargeted IAP to all versus no screening and no IAP
- screening based on culture test at 35–37 weeks versus no screening and no IAP
- rapid test 1 (PCR) versus no screening and no IAP
- routine untargeted IAP to all versus screening based on risk factors.

Figure 14 presents the cost-effectiveness acceptability curve (CEAC) for the two strategies routine untargeted IAP to all and no screening and no IAP. A CEAC is a method of illustrating the uncertainty in estimates of cost-effectiveness.¹³¹ The diagram illustrates that, in choosing between these two strategies, at a threshold below £470,000 per EOGBS-associated infant death avoided, the strategy of routine untargeted IAP to all would not be considered cost-effective and the choice of strategy would be to do nothing (i.e. no screening and no IAP). However, at a threshold above £630,000 the decision would be to choose the strategy of routine untargeted IAP to all with certainty. In between these two thresholds the choice could be either strategy if the parameters were known with certainty.

None of the other comparisons can present a strategy that would be accepted with certainty at a threshold lower than £630,000 with the exception of the final pairwise comparison between routine

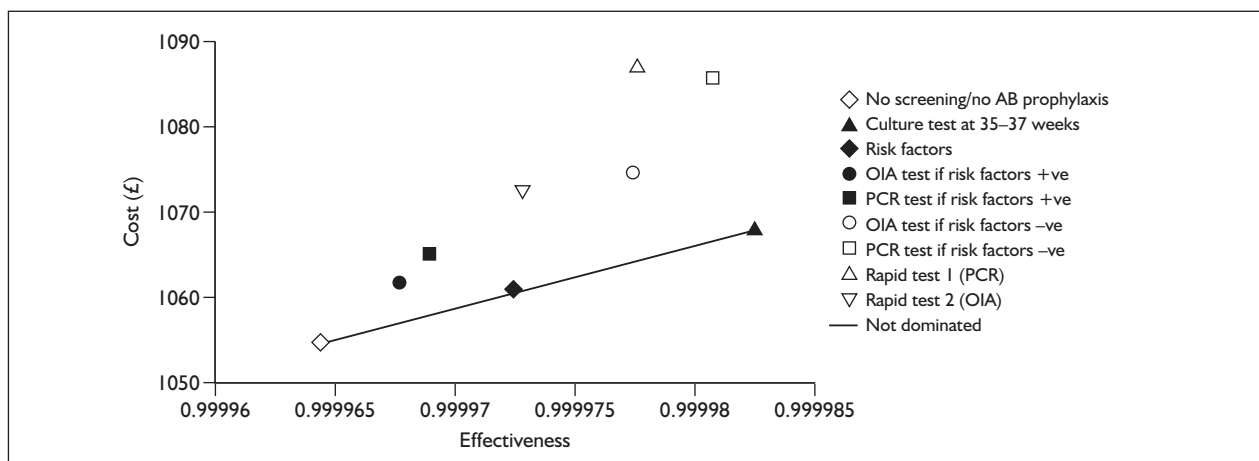


FIGURE 13 Cost-effectiveness analysis based on early-onset group B streptococcus (EOGBS) deaths avoided – routine intravenous antibiotic prophylaxis excluded. AB, antibiotic; OIA, optical immunoassay; PCR, polymerase chain reaction.

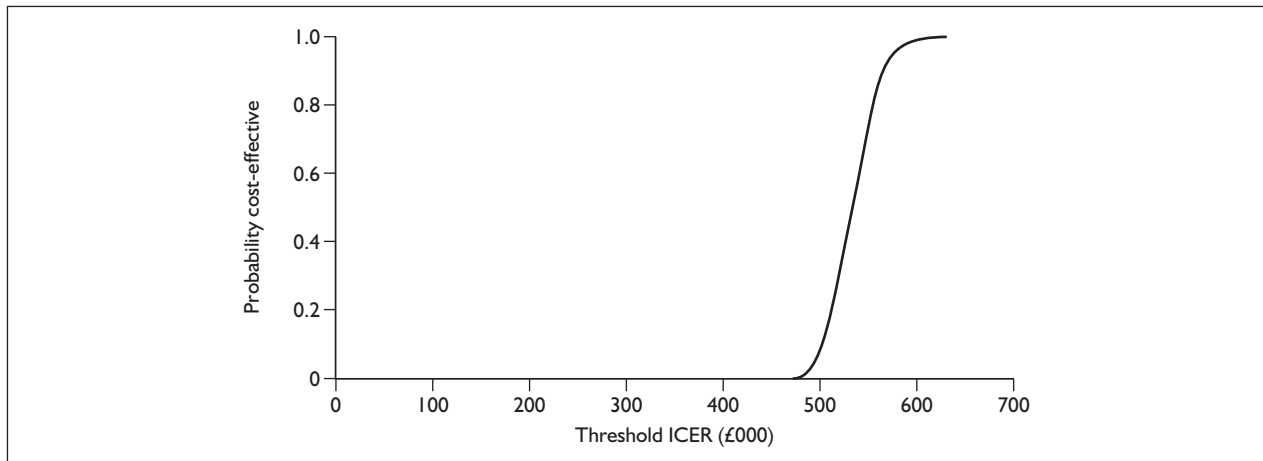


FIGURE 14 CEAC 1 – the cost-effectiveness acceptability curve for the two strategies routine untargeted intravenous antibiotic prophylaxis (IAP) to all and no screening and no IAP. ICER, incremental cost-effectiveness ratio.

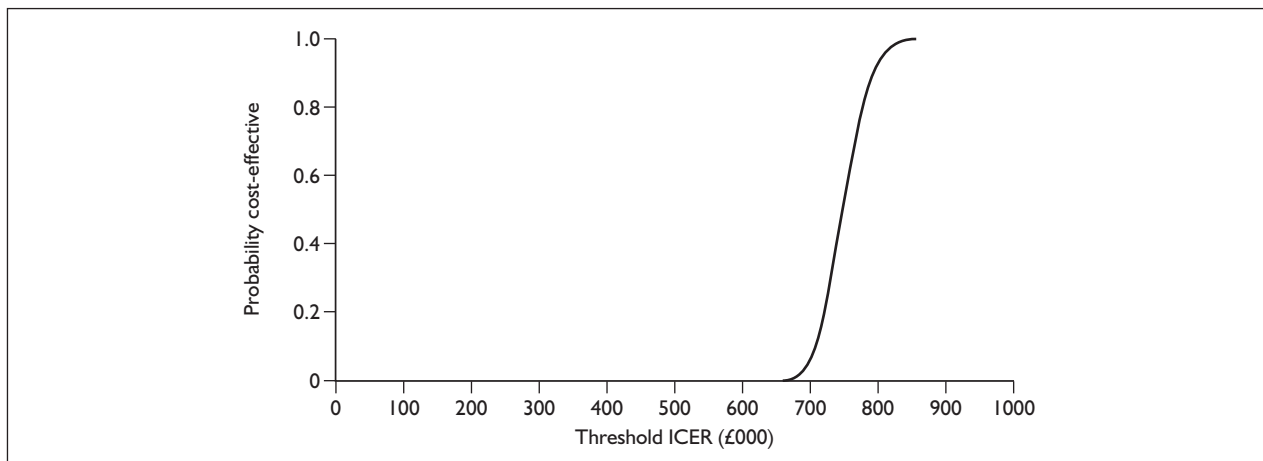


Figure 15 CEAC 2 – the cost-effectiveness acceptability curve for the two strategies culture test at 35–37 weeks and no screening and no intravenous antibiotic prophylaxis (IAP). ICER, incremental cost-effectiveness ratio.

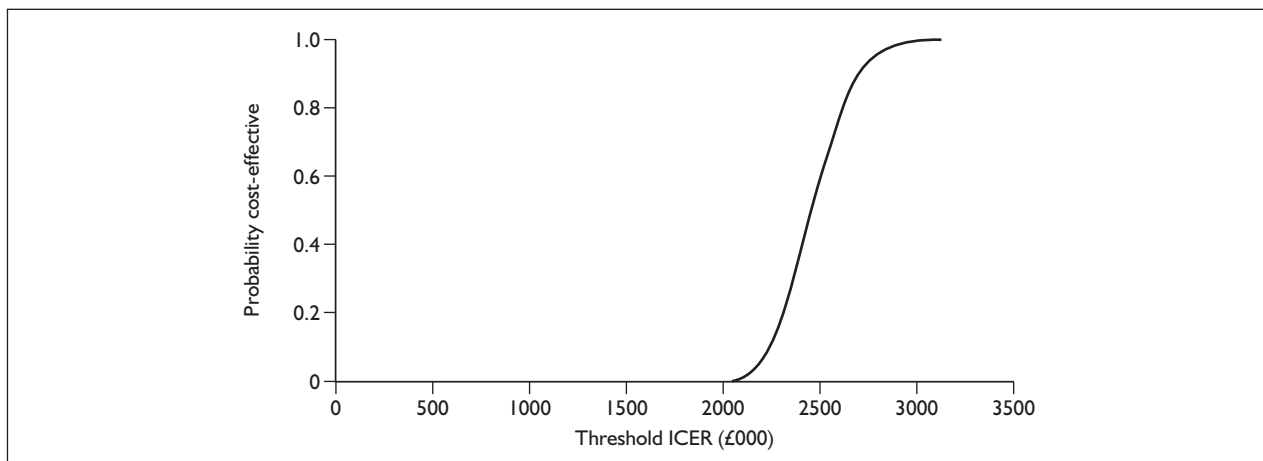


FIGURE 16 CEAC 3 – the cost-effectiveness acceptability curve for the two strategies rapid test PCR and no screening and no intravenous antibiotic prophylaxis (IAP). ICER, incremental cost-effectiveness ratio.

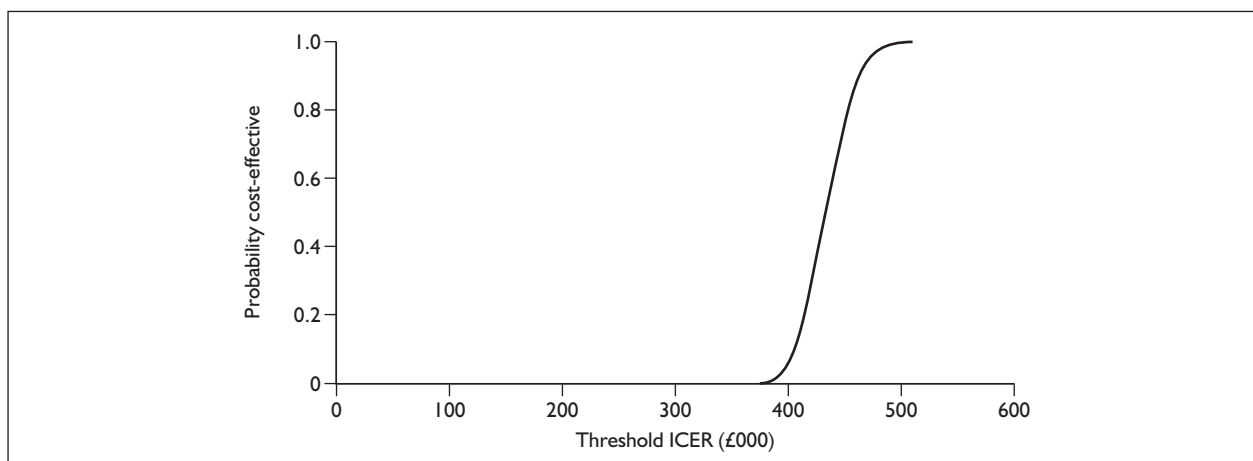


FIGURE 17 CEAC 4 – the cost-effectiveness acceptability curve for the two strategies routine untargeted intravenous antibiotic prophylaxis (IAP) to all and risk factors. ICER, incremental cost-effectiveness ratio.

untargeted IAP to all and screening based on risk factors (Figures 15–17). In this final comparison, the strategy of routine untargeted IAP would be accepted with certainty at a willingness to pay threshold of just over £500,000 (Figure 17).

Figure 16 illustrates that, in choosing between the strategies of the rapid test based on PCR and doing nothing, at a threshold below £2,000,000 per EOGBS-associated infant death avoided the strategy of the rapid test based on PCR would not be considered cost-effective and the choice of strategy would be to do nothing (i.e. no screening/no antibiotics) with certainty. However, at a threshold above £3,200,000 the decision would be to choose the strategy of rapid testing based on PCR with certainty.

Deterministic sensitivity analysis

In Tables 31 and 32 the summarised results of the deterministic sensitivity analyses are presented for analyses 1 and 2 respectively. For both analyses the results are based on an outcome of EOGBS-associated infant death avoided. A summarised set of similar sensitivity analyses based on the outcome of EOGBS disease cases avoided is presented in Appendix 8.

Changing the cost associated with EOGBS-associated infant death

In all cases and for both analyses there is no significant effect on the ICER by using different estimates for the cost of EOGBS death. Changes in these costs would not change any decision made on the basis of the base-case ICER.

Changing the cost associated with the culture test at 35–37 weeks' gestation

For analysis 1, if the cost associated with the culture test at 35–37 weeks could be reduced from its base-case estimated cost of £10.63 to £6.50, the strategy of culture at 35–37 weeks' gestation would become the preferred strategy, as the ICER for this strategy compared with doing nothing would be £532,724 per EOGBS-associated infant death avoided.

For analysis 2, when the strategy of routine untargeted IAP to all is removed from the analysis, the culture test at 35–37 weeks' gestation, which costs £10.63, becomes the preferred and most cost-effective strategy in the base case. However, for a relatively very small increase in the cost of culture, i.e. an increase of less than £1.00 to £11.50, screening based on culture is no longer the most cost-effective strategy and screening based on risk factors would be the most cost-effective strategy.

Changing the estimated effect of intravenous antibiotic therapy on EOGBS disease and infant death, given maternal colonisation

The OR used by Colbourn *et al.*⁶⁹ for the treatment effect of IAP, given maternal colonisation, was much lower [0.028 (95% CI 0.0015–0.12)] than the OR used in the base case in this model [0.17 (95% CI 0.07–0.39)]. When the OR of Colbourn *et al.*⁶⁹ is used in the current model there is a significant effect on the ICER.

For analysis 1, which includes all options, the most cost-effective strategy of routinely providing IAP to all remains the most cost-effective option but

TABLE 31 Analysis 1 – summary of the main results and sensitivity analysis in terms of cost, effectiveness and incremental cost-effectiveness ratios (ICERs), based on an outcome of cost per case of early-onset group B streptococcus (EOGBS)-associated infant death avoided

Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER per EOGBS-associated infant death avoided (£)	Approx. cost per QALY (based on discounted QALYs) (£) ^a
Base-case results ^b	1069	14.06	0.999991	0.000026	533,683 ^c	19,766 ^c
A. Changing the cost associated with EOGBS death						
£500	1069	14.09	0.999991	0.000026	534,721 ^c	19,804 ^c
£2000	1069	14.05	0.999991	0.000026	533,221 ^c	19,748 ^c
£3000	1069	14.03	0.999991	0.000026	532,221 ^c	19,712 ^c
B. Changing the cost associated with the culture test						
Culture test costs £6.50	1064	9.60	0.999982	0.000018	532,724 ^c	19,804 ^c
Culture test costs £7	1069	14.06	0.999991	0.000026	533,683 ^c	19,766 ^c
C. Changing the estimated effect of intravenous antibiotic therapy on EOGBS disease given maternal colonisation						
Alternative estimated treatment effect for antibiotics = 0.028 (OR) ⁶⁹	1069	14.00	0.999998	0.000034	413,399 ^c	15,311 ^c
D. Changing the rapid test PCR sensitivity and specificity from that based on vaginal swab only to that based on vaginal and rectal swabs combined						
Combined swabs: sensitivity = 0.84, specificity = 0.87	1069	14.06	0.999991	0.000026	533,683 ^c	19,766 ^c
E. 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 (based on vaginal swab)						
PCR test costs £4.50	1062	6.88	0.999978	0.000013	523,993 ^c	19,407 ^c
PCR test costs £5	1069	14.06	0.999991	0.000026	533,683 ^c	19,766 ^c

Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER per EOGBS-associated infant death avoided (£)	Approx. cost per QALY (based on discounted QALYs) (£) ^a
F. 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 (based on combined vaginal and rectal swabs)						
PCR test costs £6	1064	9.61	0.999983	0.000019	507,442 ^c	18,794 ^c
PCR test costs £6.50	1069	14.06	0.999991	0.000026	533,683 ^c	19,766 ^c
G. Changing the cost associated with antibiotic prophylaxis and treatment						
IAP cost £23.00	1077.000	22.78	0.999991	0.000026	864,560 ^c	32,021 ^c
IAP cost £23.50	1070.577	15.83833	0.999982	0.000018	878,761 ^c	32,547 ^c
	1078.023	7.446481	0.999991	0.000008	893,853 ^c	33,106 ^c
IAP, intravenous antibiotic prophylaxis; OR, odds ratio; PCR, polymerase chain reaction; QALY, quality-adjusted life-year.						
a Based 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.						
b For base case: cost for EOGBS-associated death is £1538; estimated effect of intravenous antibiotic therapy on EOGBS, given maternal colonisation, is 0.17 (OR based on Cochrane estimate); ⁴³ sensitivity and specificity used for rapid test PCR based on vaginal swab only are 0.584 and 0.923 respectively.						
c ICER presented compared with the strategy of doing nothing.						

TABLE 32 Analysis 2 – summary of the main results and sensitivity analysis in terms of cost, effectiveness and incremental cost-effectiveness ratios (ICERs), based on an outcome of cost per case of early-onset group *B. streptococcus* (EOGBS)-associated infant death avoided

Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER per EOGBS-associated infant death avoided (£)	Approx. cost per QALY (based on discounted QALYs) (£) ^a
Base case ^b	1068	13.43	0.999982	0.000018	745,142 ^c	27,620 ^c
A. Changing the cost associated with EOGBS death						
£500	1068	13.45	0.999982	0.000018	746,180 ^c	27,636 ^c
£2000	1068	13.42	0.999982	0.000018	744,680 ^c	27,580 ^c
£3000	1068	13.40	0.999982	0.000018	743,680 ^c	27,543 ^c
B. Changing the cost associated with the culture test						
Cost of culture test is £11	1069	13.77	0.999982	0.000018	764,172 ^c	28,303 ^c
Cost of culture test is £11.50	1061	6.12	0.999972	0.000008	764,579 ^c	28,314 ^c
Culture test at 35–37 weeks	1069	8.12	0.999982	0.00001	810,097 ^d	30,003 ^d
C. Changing the estimated effect of intravenous antibiotic therapy on EOGBS given maternal colonisation						
Alternative estimated treatment effect for antibiotics = 0.028 (OR) ⁶⁹	1068	13.38	0.999989	0.000024	549,011 ^c	20,333 ^c
D. Changing the rapid test PCR sensitivity and specificity from that based on vaginal swab only to that based on vaginal and rectal swabs combined						
Combined swabs: sensitivity = 0.84, specificity = 0.87	1068	13.43	0.999982	0.000018	745,142 ^c	27,598 ^c
E. 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 (based on vaginal swab)						
PCR test costs £7	1064	9.38	0.999978	0.000013	714,367 ^c	26,458 ^c
Rapid test 1 (PCR)	1068	4.05	0.999982	0.000005	827,762 ^d	30,658 ^d
Culture test at 35–37 weeks	1068	13.43	0.999982	0.000018	745,142	27,598
PCR test costs £7.50	1068	13.43	0.999982	0.000018	745,142	27,598

Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER per EOGBS-associated infant death avoided (£)	Approx. cost per QALY (based on discounted QALYs) (£) ^a
F. 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 (based on combined vaginal and rectal swabs)						
PCR test costs £10.50						
Rapid test 1 (PCR)	1069	14.11	0.999983	0.000019	745,060 ^c	27,595 ^c
Risk factors –ve, PCR +ve	1071	2.60	0.999985	0.000002	1,257,296 ^d	46,566 ^d
PCR test costs £11						
Culture test at 35–37 weeks	1068	13.43	0.999982	0.000018	745,142 ^c	27,598 ^c
Risk factors –ve, PCR +ve	1072	3.67	0.999985	0.000003	1,229,543 ^d	45,539 ^d
G. Changing the cost associated with antibiotic prophylaxis and treatment						
IAP cost £50						
Culture test at 35–37 weeks	1077	22.76022	0.999982	0.000018	1,262,810 ^c	46,771 ^c
H. Not giving untargeted antibiotics to all preterm babies						
Risk factors	1061	6.12	0.999972	0.000008	764,579 ^c	28,318 ^c
Culture test at 35–37 weeks	1067	6.29	0.999978	0.000005	1,168,850 ^d	43,291 ^d
Risk factors –ve, PCR +ve	1086	18.50	0.999981	0.000003	6,391,452 ^d	236,720 ^d

IAP, intravenous antibiotic prophylaxis; OR, odds ratio; PCR, polymerase chain reaction; QALY, quality-adjusted life-year.

a Based 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.

b For base case: cost for EOGBS-associated death is £1538; estimated effect of intravenous antibiotic therapy on EOGBS, given maternal colonisation, is 0.17 (OR based on Cochrane estimate⁴³); sensitivity and specificity used for rapid test PCR based on vaginal swab only are 0.584 and 0.923 respectively; base-case cost of IAP is £14.28.

c ICER presented compared with the strategy of doing nothing.

d ICER presented incrementally compared with the value presented directly above it.

the new estimated ICER is £413,399 per EOGBS-associated death avoided, which is lower than the estimated ICER in the base case.

For analysis 2, which excludes antibiotics to all as a strategy, the ICER for the most cost-effective strategy of screening based on culture at 35–37 weeks' gestation falls from £745,142 in the base case to £549,011 per EOGBS-associated death avoided, based on the alternative estimated treatment effect.

Changing the PCR rapid test accuracy from that based only on a vaginal swab to that based on rectal and vaginal swabs combined

Changing the PCR test accuracy from that derived from a vaginal swab, which was used in the base case, to that derived from rectal and vaginal swabs combined had no effect on the results.

Threshold analysis for the cost of the PCR rapid test

The cost of the PCR rapid test, based on vaginal swabs only, was estimated to be £29.95 in the current study.

For analysis 1, the threshold analysis shows that, given current accuracy in terms of sensitivity and specificity, based on the vaginal swab only, if the cost of the PCR rapid test could be reduced to as low as £4.50 then it would become the most cost-effective strategy and is likely to be accepted by decision-makers.

For analysis 2, the threshold analysis shows that, given current accuracy in terms of sensitivity and specificity, based on the vaginal swab only, if the cost of the PCR rapid test could be reduced to as low as £7.00 then it would become the most cost-effective strategy.

Threshold analysis for the cost of the PCR rapid test (based on vaginal and rectal swabs combined)

For analysis 1, the threshold analysis shows that, given current accuracy in terms of sensitivity and specificity, based on the vaginal and rectal swabs combined, if the cost of the PCR rapid test could fall to as low as £6.00 then it would become the most cost-effective strategy and is likely to be accepted by decision-makers.

For analysis 2, in which the strategy of routine untargeted IAP to all is removed from the analysis, the threshold analysis shows that, given current

accuracy in terms of sensitivity and specificity, based on the vaginal and rectal swabs combined, if the cost of the rapid test could fall to as low as £10.50 then it would become the most cost-effective strategy.

Removing the assumption that all women who deliver before the screening test based on culture at 35–37 weeks' gestation are treated with IAP (analysis 2 only)

When the assumption that all women who deliver before 35 weeks' gestation are given antibiotics is removed there is an impact on the results. The strategy of screening based on risk factors has the most favourable ICER, at £764,579 per EOGBS-associated death avoided, but may not be acceptable in terms of willingness to pay. The ICER for the strategy of culture test at 35–37 weeks' gestation changes to £1,168,850 per EOGBS-associated death avoided and would no longer be acceptable to decision-makers.

Threshold analysis for the cost of antibiotics (based on vaginal swabs only)

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 £23.50, at which stage the strategy of culture at 35–37 weeks also becomes a potentially cost-effective strategy with an ICER of £864,560. 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 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

Summary of main findings

The results of this economic evaluation suggest that the strategy of routine untargeted IAP prophylaxis to all is the most cost-effective strategy compared with doing nothing and relative to all other strategies that have been compared in this analysis. This conclusion is drawn from the ICER based on the outcome of EOGBS-associated infant deaths avoided, which has been compared with

the NICE threshold of £20,000 per QALY. The results of the full modelling analysis (based on analysis 1) estimated that the ICER for routine untargeted IAP to all compared with doing nothing was approximately £533,000 per EOGBS-associated infant death avoided. Assuming that a surviving infant would be in full health and that a life in full health, discounted at the discount rate recommended by NICE of 3.5%, is worth approximately 27 discounted QALYs, the estimated ICER is £19,766 per QALY. Thus, this strategy is likely to be accepted by NICE on cost-effectiveness grounds alone.

When the results of the model were evaluated based on an outcome of EOGBS disease avoided, routine untargeted IAP to all was again the most cost-effective strategy compared with doing nothing and relative to all other strategies. The corresponding ICER was estimated to be £39,813 per case of EOGBS disease avoided compared with a strategy of doing nothing, but this ICER is less easy to interpret for decision-making.

When the strategy of providing antibiotics to all is removed from the model in analysis 2, the most cost-effective strategy was the culture test at 35–37 weeks' gestation compared with doing nothing and relative to all other remaining strategies. Based on the assumptions of full health and discounted QALYs as described previously, the ICER for culture at 35–37 weeks' gestation compared with doing nothing was approximately £745,000 per EOGBS-associated infant death avoided, which translated to £27,620 per QALY. This exceeds the acceptable threshold set by NICE of £20,000 per QALY and thus would not be automatically accepted on cost-effectiveness grounds alone. Therefore the uncertainty surrounding this estimate would require greater scrutiny. If the assumption that surviving infants would survive in full health was considered plausible, then the strategy is more likely to be accepted. If the assumption that survivors would experience full health was thought not to be plausible, then the strategy is likely to be rejected and doing nothing would be the recommended strategy based on the current evidence.

These results, for both analysis 1 and analysis 2, were shown to be robust for the majority of sensitivity analyses. However, there were two main exceptions. First, it was notable that changing the estimated effect of intravenous antibiotic therapy on EOGBS disease given maternal colonisation, resulted in a significant effect on the ICERs in

both analyses, which served to make the most cost-effective ICER for each analysis even more favourable relative to the NICE threshold. Second, in analysis 2, when either the cost of the culture test was increased by a small amount, or the base-case assumption that women who gave birth before receiving the screening test based on culture at 35–37 weeks' gestation were given intrapartum antibiotics was removed, and it was instead assumed that none of these mothers received intrapartum antibiotics, screening based on risk factors became the most cost-effective strategy and the strategy of screening based on the culture test at 35–37 weeks' gestation was no longer a contender in the results at all.

Strengths of the methods used

The strength of this analysis is that the majority of the data used to populate the options in the model is based on the latest empirical data from the current primary study in particular cost and resource data associated with the strategies of the rapid test, providing antibiotics and screening based on risk factors were carefully monitored prospectively as part of the primary study. The costs and resources associated with performing the screening test based on culture were also recorded, although in this analysis we used culture at delivery as a proxy for the costs and resources associated with the culture test at 35–37 weeks' gestation. The effectiveness data for the accuracy of the rapid test, risk factor-based screening and culture were also empirically evaluated during the study.

The model used was comprehensive and compared all of the options that are available to date. Although some studies have evaluated the use of vaccination for GBS, there is currently no licensed vaccine available.

Limitations of the study

In the main analysis, providing routine untargeted IAP to all is shown to be the most cost-effective option. However, the full cost associated with this strategy is likely to have been underestimated. This is primarily because the model has not included any costs associated with potential resistance to antibiotics or side effects in this population, both of which could lead to complications for the woman or baby later on. Furthermore, if policy were to change in favour of this strategy, then the capacity available in labour wards would have to be expanded as more women would be required to give birth in hospitals or birthing centres that

are equipped to provide intravenous antibiotics. The additional demand and its impact on costs to hospitals and delivery units have not been incorporated into the current analysis. Added to this is the likelihood that such a strategy would not be acceptable to the majority of women who are anxious and resist the further medicalisation of childbirth.

In analysis 2, which specifically excluded the strategy of routine untargeted IAP to all, the strategy of a culture test at 35–37 weeks' gestation for all women was shown to be the most cost-effective option. This strategy included the assumption that women who went into labour before undergoing this test would receive routine antibiotics; when this assumption was removed from the analysis the strategy of screening based on risk factors became the most cost-effective option. Furthermore, it is likely that the costs associated with the strategy of a culture test at 35–37 weeks' gestation will also have been underestimated, and it too is a strategy that will impinge on the way that women have traditionally been cared for. Similar to the strategy of providing routine untargeted IAP to all, it will be necessary for large numbers of midwives to be trained in the prescribing and administration of intravenous antibiotics. There are also likely to be late changes to women's plans for delivery, which will in turn have capacity issues.

Although there exist some limited data on survival and quality of life for infants who experience this disease, given the current available lifesaving technology that can assist infants who are born preterm and/or who experience EOGBS disease, there is no concurrent evidence on the quality of life experienced by the infants who do survive.^{21,132} The outcomes presented in terms of cost per QALY in the current study have been estimated based on available guidelines on discounting and known acceptable thresholds for decision-makers and not on quality of life data.

Finally, in terms of limitations, it is not clear or possible to determine exactly what constitutes current practice for the prevention of EOGBS disease in infants in the UK. The main comparator for the economic evaluation has been to do nothing, and the model has been calibrated to the population prevalence of neonatal EOGBS disease and EOGBS-associated 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.¹³³

Interpretation of the findings

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' gestation, with antibiotics given to all those women who deliver before 35 weeks, becomes the most cost-effective option.

The results of the analysis have shown that the rapid test in its current form, either PCR or OIA based on vaginal or rectal swabs, does not offer a cost-effective alternative option for screening women to assess colonisation by GBS.

In analysis 1, for the rapid test to become a more favourable strategy than antibiotics, given its current accuracy, it would have to cost as little as £6.00 based on the combined rectal and vaginal swabs and as little as £4.50 based on the vaginal swab alone. In analysis 2, the corresponding costs required of the rapid test in order for it to become a more favourable option than screening based on culture at 35–37 weeks' gestation are £10.50 and £7.50. These costs contrast sharply with the current cost of the rapid test, which is approximately £29.50.

Comparison with other studies

In the study by Colbourn *et al.*⁶⁹ a model was developed for use in the economic evaluation of prenatal screening and treatment strategies to prevent GBS disease in early infancy. Key differences between the results of the study by Colbourn *et al.* and those of the current study include that their results were reported in cost per QALYs and their analysis attempted to incorporate the adverse effects of antibiotic use. They also used a different estimated effect of intravenous antibiotic therapy on EOGBS disease and death given maternal colonisation – OR 0.028 (95% CI 0.0015–0.12) – which was much lower than the one reported in the Cochrane library.⁴³ The justification for the use of the alternative estimate by the authors is based on opposing schools of thought regarding the use of a fixed-effects estimator in meta-analysis. Colbourn *et al.* argue that the Cochrane estimate is based on the Peto one-step method,¹³⁴ which is a fixed-effect estimator, which they assert produces 'seriously biased estimates when the true treatment effects are large (as in the present analysis)' (references 124 and 125 in their report). Our sensitivity analysis showed that when the alternative estimate was used there was a

significant impact on the results, which made the relative ICERs more favourable.

The strategies compared were broadly very similar, although Colbourn *et al.* divided the population into specific risk groups and also included vaccination against GBS as a strategy for comparison in their model, which was not included in the current analysis.

Overall, the results of the analysis by Colbourn *et al.* were broadly similar to those reported here. They showed that screening based on risk factors and screening based on the rapid test were not cost-effective strategies. Vaccination was shown to be 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' gestation was found to be cost-effective for low-risk women.

Recommendations for practice

The results show that, based on current evidence, neither rapid test, as evaluated in the current study, should be used in practice as it is clearly not a cost-effective method of screening women for GBS colonisation.

There is some evidence to support the serious consideration of the strategies of providing routine untargeted antibiotics prophylactically to women and of testing women at 35–37 weeks' gestation based on culture of vaginal and rectal swabs, with antibiotics provided to women who deliver before 35 weeks.

Recommendations for research

There is a clear need to develop a simple point-of-care test that has a high level of accuracy compared with the gold 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. The costs of screening by culture at 35–37 weeks' gestation have been based on the costs of the reference standard and may not reflect the true costs of this strategy. These could only be derived with more accuracy by conducting a feasibility and costing study in a hospital setting. Future modelling should consider this.

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.

Chapter 5

Discussion

Introduction

This HTA project completed three distinct pieces of work:

- to determine the accuracy (sensitivity, specificity, predictive values) of PCR and OIA technologies as rapid tests for maternal vaginal and rectal GBS colonisation at the onset of labour using selective enrichment culture as the reference standard in a primary study
- to determine the acceptability of rapid testing for GBS colonisation among pregnant women of different social and ethnic groups in a primary study
- to determine the cost and cost-effectiveness of rapid intrapartum testing for maternal GBS colonisation to prevent EOGBS disease, and to compare this with other strategies for screening and prevention using a decision-analytic model.

Each of these has been described in detail and the main findings reported and the conclusions discussed in the light of any limitations identified at the end of each of the three preceding chapters. This chapter attempts to focus on the key findings and limitations emerging from all of the work undertaken. It is not a comprehensive summary of all of the issues raised, for which the reader is encouraged to consult the previous three chapters.

Group B streptococcus is the leading cause of serious neonatal sepsis with the majority of cases of EOGBS disease occurring within 24 hours of delivery. Maternal colonisation of the vagina and lower gastrointestinal tract is common and, if untreated, GBS can be transmitted during delivery to the neonate with potentially fatal consequences. Any prevention strategy must be directed towards reducing intrapartum transmission, as treating EOGBS disease once established is unlikely to be fully beneficial. In the UK, the policy since 2001 has been based on the assessment of women during labour for the presence of one or more known risk factors, described in Chapter 1 (see Risk factors for neonatal GBS disease). IAP with penicillin or clindamycin is then offered to those with risk factors. However, in the USA and elsewhere,

screening involves the culture of vaginal and rectal swabs from all women at between 35 and 37 weeks' gestation, and IAP is offered to those in whom GBS is detected and usually also in preterm deliveries when GBS culture results are unavailable.

Several non-culture-based tests are available that could be developed into rapid point-of-care diagnostic tools for intrapartum screening. This would allow optimal targeting of IAP to women carrying GBS during labour. This project evaluated two rapid tests – PCR and OIA – in terms of their accuracy, feasibility, acceptability and cost-effectiveness for their potential to be introduced as a routine screening test in labour and delivery suites.

Evaluation of the rapid tests

The accuracy of the PCR and OIA tests, using vaginal and rectal swabs, was estimated in a primary test accuracy study, using enriched culture of contemporaneous swabs from the same sites as the reference standard. A positive culture from either site was considered to be indicative of maternal colonisation, as transmission to the neonate could occur from either site during delivery. Index test results derived by using vaginal or rectal swab results were more sensitive than either test considered individually, although at the expense of a decrease in specificity. The best accuracy was obtained using vaginal or rectal PCR rapid test results, giving a sensitivity of 84% (95% CI 79–84%) and specificity of 87% (95% CI 85–89%). PCR was significantly more accurate than OIA for all test combinations, reproducing the findings of a meta-analysis of rapid tests.³⁵ However, PCR took longer to perform, providing a result after a median time of 80 minutes compared with 35 minutes for OIA, and failed to produce a result more often (see Appendix 3).

In this study the presence of any one of the five known risk factors proved poorly predictive of maternal colonisation, with a sensitivity of 31%, which is much lower than that reported previously. The probabilities of maternal colonisation were calculated by logistic regression, based on

prevalence and test result; the presence or absence of maternal risk factors did not significantly alter the post-test probability. There was variation in test accuracy in the presence or absence of risk factors, with sensitivities generally higher in the presence of risk factors and specificities higher in their absence. Differences were generally small and there was no general pattern as to which test–reference combinations were statistically different. So, although there was some variation in test characteristics according to presenting characteristics, the impact on predictive probabilities was not large. Multiple logistic regression demonstrated that a positive rapid PCR test significantly increased the odds of neonatal colonisation, whereas sufficient IAP significantly reduced the odds. There were insufficient cases of EOGBS disease to determine predictors of disease.

Most women in the study felt that the test was important and would be happy to be treated on the basis of the test result, with those at highest risk being most accepting. However, women were less comfortable and more embarrassed about rectal swabs than vaginal swabs, and South Asian women in particular found rectal swabbing less acceptable. Thus, although the economic model investigated the most accurate index test–reference standard combination, using the combined vaginal and rectal test results, this may not adequately reflect the actual take-up of the screening test if implemented. Because of this concern the base-case cost-effectiveness analysis used rapid tests of vaginal swabs only.

Given that it is recommended that IAP be given for at least 2 hours, and preferably 4 hours, before delivery for maximum effectiveness in reducing transmission, slower tests will result in fewer mothers receiving adequate IAP. The proportion of mothers in the study for whom rapid test results were available with hypothetically sufficient time to provide IAP, based on the median test time and length of labour, was used in the economic model. This model parameter assumes that clinical staff are able to act swiftly on the results of the rapid test and that mothers accept IAP if indicated by test results. The former was not assessed in this study as results were not made available to health professionals to inform treatment and also because most index tests were not performed in ‘real time’.

The testing process itself was safe for the mothers and capable of being performed by midwifery assistants after suitable training. This staff group was chosen because it was considered

that midwifery assistants would be more readily available to undertake testing on demand, and some were already undertaking point-of-care tests. However, if rapid testing was introduced into routine care, midwives indicated that they would see it as part of their professional responsibilities to perform the test and act on the results. The costs for the rapid tests incorporated into the economic model were based on midwives undertaking the testing.

Strengths and limitations

The 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 of the superiority of PCR over OIA are valid. We minimised methodological bias by ensuring that the index tests and reference standard were performed independently and interpreted blind to each other. Also, the triple swab used in this study was designed to ensure that the index and reference tests were undertaken on contemporaneous samples. The fact that the rate of detection of GBS using the reference test was at least as high as in previous reports suggests that the sample quality in our study was adequate. There was also a very high proportion of index test verification by reference standard; over 96% for PCR. We investigated the effect of spectrum bias by collecting data on characteristics of the sample and assessing variability across various spectra. A sample size calculation was performed to ensure that the study had sufficient power to exclude a clinically unacceptable accuracy and the study recruited to that target. The large sample also provided the opportunity to analyse the influences of demographic and other variables on satisfaction with, and acceptability of, different aspects of testing.

However, the study sample may not be truly representative of a typical UK maternity population, which may limit generalisability. Many women who were approached did not agree to take part, leading to inevitable biases in the sample. Women from South Asian ethnic origins were under-represented in the sample of those swabbed, for various reasons including language barriers. As this group was generally more negative about rapid testing than most other ethnic groups, the overall acceptability of the test is likely to be overestimated. Premature deliveries were substantially under-represented in the study sample, whereas emergency Caesarean section

and induced deliveries were over-represented. There were fewer women presenting with known risk factors compared with previous studies, as staff tended to avoid asking women in premature labour, to avoid additional anxiety for the mother. Another important consideration is that the study was undertaken amongst women from two urban populations booking for delivery in consultant-led birth units. As such it cannot be assumed that the attitudes of women in this survey are representative of the entire maternity population.

The primary study was not designed to assess the consequences of rapid test results and no woman was treated on the basis of the test result. Participants' views on acceptability, although based on a real experience, were only relevant to the testing process, as they may not have realised what treatment would have involved. Alternative methods of preventing GBS transmission were not discussed with the women involved in the study and so they could not give their views on their preferences for screening in late pregnancy, the administration of universal prophylactic antibiotics or the possibility of a vaccination being developed to be taken during pregnancy. Lack of knowledge of the treatment regime and alternative screening strategies may have influenced their views on satisfaction with information and the acceptability of rapid testing in routine care.

Test results may not be as consistently and rapidly obtained when employed in a point-of-care situation and conducted by staff providing usual care to labouring women. In our study fewer tests were performed in real time as the study progressed, with the majority of tests performed in batches by the research staff. There were several reasons for this including high staff turnover, delays in recruitment and competing demands on the time of the trained midwifery assistants. The risk of being unable to obtain results in real time was a concern that was widely expressed by midwives involved in the study.

Cost-effectiveness of rapid testing compared with other screening strategies

Having determined the accuracy of the two rapid tests, and explored the acceptability of testing to mothers and midwives, the study then determined the cost of rapid testing and finally examined the cost-effectiveness of rapid testing compared with other screening and treatment strategies.

A decision-analytic model was used, taking the perspective of the UK NHS, and the primary outcomes were the costs per case of EOGBS disease and associated infant death avoided.

The strategies considered were untargeted IAP to everyone, treatment based on culture of vaginal and rectal swabs taken at 35–37 weeks' gestation, treatment based on either rapid test, treatment directed by the presence of risk factors or treatment based on a combination of either rapid test and risk factors. These strategies were compared with a policy of no screening and no treatment (do nothing).

The results of this economic evaluation suggest that the strategy of routine untargeted IAP to all is the most cost-effective strategy compared with doing nothing and relative to all other strategies compared, costing £533,000 per EOGBS-associated infant death avoided. If this is translated into cost per QALY using estimates of QALYs for full health and discount rates recommended by NICE, the estimated ICER was £19,766 per QALY. Thus, this strategy is likely to be accepted by NICE on cost-effectiveness grounds, being just under their threshold of £20,000. However, considering the outcome of case of EOGBS disease avoided, the corresponding ICER was estimated to be £39,813 compared with a strategy of doing nothing, which is less likely to be acceptable. The lack of explicit thresholds for results presented in natural units, such as disease avoided, makes such results difficult to interpret. Acceptability will depend on whether exposure to the disease has long-term complications for the majority of infants or exposes them to only transient effects and costs. Evidence on the quality of life of infants who have experienced GBS disease is required.

There are many reasons why a policy of routine IAP might be deemed unacceptable. Midwives involved in the study, who discussed the alternatives to rapid testing, were extremely opposed to universal administration of antibiotics to prevent GBS transmission and believed that mothers would be too. Implementation of such a policy would require considerable reorganisation of maternity services to facilitate the administration of intravenous antibiotics and would run contrary to the new government policy of choice in maternity care and availability of home birth or delivery in midwife-led centres.¹³⁵ There are significant uncertainties around the microbiological risks posed by a strategy of widespread antibiotic use, albeit the number of doses per patient would be low. Large-

scale exposure to benzyl penicillin is unlikely to promote resistance in GBS, but the same is not true of clindamycin.¹³⁶ Either antibiotic might increase the risk of superinfection of mothers and/or babies with micro-organisms other than GBS,^{137,138} whereas insertion of intravascular devices for administration of intravenous antibiotics might be an independent risk factor for infection. There is also a possible risk that increased antibiotic use could promote the spread of *Clostridium difficile* and other nosocomial pathogens.

The decision-analytic model was therefore reanalysed, removing the strategy of routine untargeted IAP from the model. The most cost-effective strategy was then to screen by culture of vaginal and rectal swabs at 35–37 weeks' gestation, relative to all other remaining strategies and compared with doing nothing. Based on the assumptions of full health and discounted QALYs as described previously, the ICER for culture at 35–37 weeks' gestation compared with doing nothing was approximately £745,000 per EOGBS-associated infant death avoided, which translated to £27,620 per QALY. This exceeds the acceptable threshold set by NICE of £20,000 per QALY and thus would not be automatically accepted on cost-effectiveness grounds alone.

Underlying the model are uncertainties regarding costs and effectiveness. One of the more tenuous is that all survivors of EOGBS disease would regain full health. Significant long-term morbidity, including impaired psychomotor development, has been reported in up to 30% of survivors.²¹ Hence, the strategy of culture tests at 35–37 weeks' gestation is likely to be rejected and doing nothing would be the recommended strategy based on current evidence. Once again, the most cost-effective strategy will not be acceptable, as it would be seen as a retrograde step from the current policy.

These results, both with and without the routine IAP strategy, were shown to be robust for the majority of sensitivity analyses around other parameters. In considering the model without routine IAP, when either the cost of the culture test was increased by a small amount or when the assumption that all deliveries before 35 weeks' gestation received IAP was changed to not treating premature deliveries, risk factor-based screening became the most cost-effective strategy. In reality, the cost of the culture test at 35–37 weeks' gestation is likely to be higher than that assumed in the current study, as the model assumed that all tests

would be performed in hospital, as they were for the reference standard, and transportation costs, for example, were not included.

Another study, by Colbourn *et al.*,⁶⁹ conducted an economic evaluation of prenatal screening and treatment strategies to prevent neonatal EOGBS disease. Key differences in model structure and inputs in this study compared with our study include the results being reported as cost per QALY, the incorporation of the adverse effects of antibiotic use in the analysis and the use of a different estimate of the effect of IAP on EOGBS disease and death given maternal colonisation. Despite this the results of the analysis by Colbourn *et al.*⁶⁹ were broadly similar to those reported here. They showed that screening based on risk factors or on either rapid test was not a cost-effective strategy. Vaccination was shown to be 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' gestation was found to be cost-effective for low-risk women.

Implications for practice

Given the generally low sensitivity of the OIA test system evaluated, a practical recommendation for clinicians when making a decision about the use of intrapartum antibiotics is not to use OIA as a test for maternal GBS colonisation. If an intrapartum rapid test is to be considered for practice then PCR appears currently to be the most accurate test.

As this study was not an RCT of alternative strategies, no direct comparisons of overall effectiveness and acceptability can be made, and relative effectiveness has to be estimated by a decision-analytic model. However, there are some features of current care that could be improved, and some recommendations to be made about the introduction of rapid testing if the technology continues to develop. The first is that midwives need to be better educated about GBS and the treatment for it. This will promote greater adherence to current guidelines and enable midwives to better inform women. For women to be able to make informed choices about their care, information needs to be given about GBS closer to the time at which testing and treatment

can be carried out. Giving information early in pregnancy, when women have many decisions to make, means that it is likely to be forgotten. If testing for GBS during the late stages of pregnancy or during labour is to be introduced, processes for the communication of results need to be improved. It is also possible that models of intrapartum care would have to be altered to facilitate both microbiological testing and the administration of intravenous antibiotics to a larger proportion of the maternity population than is currently the case. If testing was to be conducted during labour, careful consideration would need to be given to ensuring that the testing procedure fits into midwifery practice and that sufficient trained testers are available at all times to ensure that the turnaround of results is reliably timely.

The results of our economic analysis demonstrate that neither rapid test should yet be used in practice as neither is clearly a cost-effective method of screening women for GBS colonisation. There is some evidence to support serious consideration of the strategy of providing routine untargeted antibiotics prophylactically to women and the strategy of testing at 35–37 weeks' gestation based on culture, with IAP provided to all women who deliver before 35 weeks. The implications highlighted in this section, and the findings of previous chapters, should be borne in mind by policy-makers.

Recommendations for research

This study suggests that there is enough support for GBS testing during labour from midwives and women for the rapid tests to be developed further. There exists already an improved PCR system, GeneXpert® (Cepheid; Sunnyvale, CA, USA), which has minimal preparatory steps and has test kits developed for GBS. Unfortunately this system was not available during the course of this study. The evaluation of this, or any other test system, should follow a robust design for test accuracy studies with sufficient power to estimate test sensitivity over and above that achieved by the PCR tests used in this study. To be cost-effective the test would need to be both cheaper and more accurate. Any new test would need to be much simpler, to enable it to be performed as a point-of-care test in routine practice, and also quicker than the current kits available. This would improve the effectiveness of rapid tests by increasing the proportion of women for whom test results would be available in time.

Should a demonstrably cheaper, quicker and more accurate test become available, more research would still be required to demonstrate its superiority over the current policy of risk factor-based screening. This might take the form of an RCT to establish effectiveness, most likely a cluster RCT in which maternity units are randomised to one or other strategy. The feasibility of a screening policy based on culture of swabs taken at 35–37 weeks' gestation would need to be piloted before any large-scale evaluation against other strategies, as it is a departure from UK practice; however, it would provide realistic costs for further modelling. Ideally, the outcome would be cases of neonatal EOGBS disease observed but, as the incidence of disease is very low, this would require an extremely large trial with many participating units, which may be prohibitive. A good surrogate for EOGBS disease would need to be developed for any future trials.

Many women did not take part in this study because of language barriers. It is important that groups of women are not disadvantaged through non-inclusion in research. In future studies midwives should be encouraged to assess the communication skills of potential participants and other barriers to participation more formally.

GBS screening is different from any other screening test that is currently offered to pregnant women in the UK in that the methods of specimen collection are more invasive and the number of women whose labours would be medicalised would be many times higher than is currently the case. Moreover, whereas most other screening tests provide reassurance to over 99% of women tested that they present no risk to their babies, GBS screening would be expected to identify that over 20% of women do present an (albeit low) risk to their babies. More research is needed on the views of a wider cross-section of pregnant women and mothers who would be affected by GBS screening during pregnancy and labour. Compared with other areas of antenatal and perinatal screening, very little research has been undertaken on women's beliefs about GBS, including the risks it presents to their and their babies' health, whether they would welcome testing during pregnancy, including home testing or testing during labour, and their attitudes to greater medicalisation of labour. More research is also needed on the views of midwives on routine testing during labour.

The procedure for collecting samples for the rapid tests employed in the study are largely acceptable

to women and midwives, although vaginal swabs were preferred by both groups to rectal swabs. Whether accuracy would be comparable if women took samples themselves has not been evaluated, nor whether women would or could reliably take samples themselves.

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.

Should rapid testing technology be developed to a position in which it is more cost-effective than any

other strategy, further research would be required to determine how a policy of rapid testing could be universally implemented in the NHS. This would require appraisal of the management of women in delivery situations such as home births and small midwife-led units where rapid point-of-care testing and/or the facility to administer intravenous antibiotics are not available.

In a methodological context, the extent to which cost-effectiveness threshold analysis can be developed to inform sample size estimation in test accuracy studies needs to be investigated. More work and discussion are required to establish the models of independent monitoring of test accuracy studies and stopping rules.



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Contribution of authors

Jane Daniels (Research Fellow, Health Technology Assessment) managed the project, performed the test accuracy analysis and was responsible for preparing Chapters 1, 2 and 5.

Khalid S Khan (Consultant in Obstetrics, Gynaecology and Clinical Epidemiology) and James Gray (Consultant Microbiologist) designed the test accuracy study, provided clinical direction, supervised the test accuracy analysis and edited the complete report.

Helen Pattison (Senior Lecturer, Health Psychology) designed the acceptability evaluation, supervising Nicola Elliman (Research Associate, Psychology) in the analysis, and together they prepared Chapter 3.

Billingsley Kaambwa (Research Fellow, Health Economics) conducted the cost-effectiveness analysis under the supervision of Tracy Roberts (Senior Lecturer, Health Economics) and Stirling Bryan (Professor of Health Economics), who both designed the economic evaluation. Together, they prepared Chapter 4.

Elizabeth Edwards (Birmingham) and Lisa Spicer (Barking) were the coordinating research midwives for the study at each centre, implementing the protocol and collecting and cleaning the data. Philip Milner (Birmingham) was the biomedical scientist who refined the rapid tests for point-of-care use and who was responsible for training in rapid tests and laboratory cultures. Together, they prepared Appendices 1 and 2.

Robert K Hills (Principal Statistician) and Richard Gray (Professor of Medical Statistics) helped design the study and oversee the interim analyses of test accuracy by Laura Buckley (née Gross) (Statistician). The study was coordinated by Elisabeth King (née Hawker) (2004–5) and Laura Magill (2006–7). They ensured that the protocol

was implemented and prepared data for analysis and reporting.

Peter Thompson (Birmingham) and Richard Howard (Barking) are Consultant Obstetricians,

contributing to the design of the study. They were responsible for clinical supervision of the study at each centre.



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Appendix I

Standard operating procedures for rapid tests

Polymerase chain reaction test

The Smart GBS[®] kit and SmartCycler[®] system (Cepheid; Sunnyvale, CA) is a PCR kit system that can be run using Lim broth cultures or directly from vaginal/rectal specimens, using real-time PCR technology to detect GBS even in lightly colonised specimens (www.cepheid.com/Sites/cepheid/content.cfm?id=188).

Equipment

The following equipment is needed:

- Smart GBS[®] PCR kit
- SmartCycler[®]
- PC with SmartCycler[®] software
- heating block
- cooling blocks
- vortex with attachments
- centrifuge
- micropipettes
- scissors
- disposable gloves
- discard jar
- pipette tips
- timer.

Method

The method can be divided into two sections: specimen preparation and the assay protocol.

Specimen preparation

1. Break the swab or cut it with scissors into the sample buffer tube and replace cap.
2. Stand for 5 minutes.
3. Vortex tube for 15 seconds.
4. Pipette 50 µl of cell suspension into the lysis tube.
5. Vortex tube for 5 minutes.
6. Briefly centrifuge the tube to bring the contents to the bottom.
7. Heat the lysis tube to 95°C for 2 minutes then cool.

Assay procedure

1. Cool the master mix and positive and negative controls.
2. Add 25 µl of diluent to all, being careful not to touch the optical detection windows.

3. Add 1.5 µl of each lysate to the appropriate master mix tube.
4. Centrifuge tubes for 5–10 seconds and then cool.
5. Click on 'Create new run' on the SmartCycler[®] software and enter details as appropriate.
6. Before loading the tubes onto the SmartCycler[®] take the cooling block with the tubes still in place and vortex upside down for 5–10 seconds.
7. Insert each tube into the appropriate I-CORE module of the SmartCycler[®] and start run.

Interpretation of results

- IC = internal control.
- NA = not available.
- ND = not determined.
- * = refer to SmartCycler[®] software manual for interpretation of warning and error codes.

Limitations of the procedure

- There are as yet no published reports of group B streptococci without the *cfb* gene; however, if these were present, then the assay would yield a false-negative result.
- Because of the high analytical sensitivity of the test, great care is required not to contaminate the reagents.
- The sensitivity of the test is dependent upon the number of organisms present, with very low numbers resulting in negative results.
- Poorly taken swabs will result in false-negative results.
- Unresolved or invalid tests will result in the test having to be repeated, which will obviously negate the rapidity of the test.
- The test has been evaluated only on vaginal/rectal swabs so far; therefore, the assay should not be used to evaluate group B streptococcus colonisation/infection from specimens from other sources.

Interfering substances

Many substances have the potential to inhibit the PCR reaction including amniotic fluid, vaginal secretions, meconium, faeces, blood and urine. The test is, however, fairly robust, with one large study (803 specimens) showing only 1% of unresolved

specimens, of which only one remained unresolved after repeating the freeze/thaw stage.

Hazards

Swabs may be processed on the bench using recognised aseptic techniques. If any material off the swab or any chemical reagent is accidentally splashed into the eye then the eye must be washed liberally with a standard eye wash provided. Caution is also required when using the heating block as the temperature required (95°C) will cause burning.

Precautions to be used with the kit

- Close the protective pouches of the master mix and controls quickly with the zip seal after each use.
- Reagents are not interchangeable between lots.
- Never pool reagents from different tubes even if they are from the same lot.
- Do not use reagents after their expiry date.
- Do not interchange caps among reagents as contamination may occur and compromise test results.
- Avoid microbial and deoxyribonuclease contamination of reagents when removing aliquots from tubes. The use of sterile deoxyribonuclease-free pipette tips is recommended.
- To avoid contamination of the environment with group B streptococcus amplicons, do not open the reaction tubes post amplification.

Optical immunoassay test

The BioStarOIA STREP B[®] test (Inverness Medical; Princetown, NJ) provides rapid detection of group B streptococcal antigen directly from cervical or vaginal swabs by a simple optical immunoassay (www.invernessmedicalpd.com/poc/products/oia_strepb.html)

Equipment

The following equipment is needed:

- BioStarOIA STREP B[®] kit with test devices (plates)
- micropipettes
- scissors
- disposable gloves
- discard jar
- pipette tips
- timer.

Methods

1. Add three drops of reagent 1A to extraction tube. Mix thoroughly to dissolve the dried

reagent at the bottom of the tube. Place the swab to be tested into the tube, thoroughly mix and hold at room temperature for 3–5 minutes.

2. Hold swab to the side of the tube while adding three drops of reagent 1B. Use swab to thoroughly mix reagents. Solution colour should change to yellow. Allow swab to stand in extraction mixture for 3–5 minutes.
3. Hold swab to side of the tube while adding three drops of reagent 2. Use swab to thoroughly mix reagents. Solution colour should change to green. Squeeze side of the tube and gently rotate the swab as you withdraw it, to leave behind as much liquid as possible in the tube. At this stage compare the volume in the tube with that on the diagram on the procedure card. If the volume does not equal or exceed the illustrated level, return the swab to the tube and add one to two extra drops of reagent 2, mix thoroughly with swab and squeeze the tube to express the solution.
4. Add three drops of reagent 3 to the extracted sample; mix thoroughly with the transfer pipette. This solution must not be allowed to stand for more than 5 minutes.
5. Using the transfer pipette place two drops of this solution centrally on the test surface of the kit. Wait for 10 minutes.
6. Wash test surface vigorously with the wash solution, taking care not to exceed the capacity of the surrounding test surface. Note: Vigorous washing will aid in obtaining a clean test surface. Insufficient washing may leave debris that may result in a faint ring surrounding the positive internal control dot. This should not be interpreted as positive because of the lack of colour shading within the ring area.
7. Confirm blotter is in position 1 in the test device lid. Close test device at corners and leave closed for 10–15 seconds. Note: Blot with a clean surface each time blotting is required. Blotter should be in position 1 when blotting for the first time. If in position 2, move to position 1 for the second blot. Repeated blotting in the same position may compromise test results.
8. Open lid, change blotter to position 2 and apply one drop of substrate centrally on the test surface. Wait 5 minutes. Note: Do not cover the entire surface of the test device with substrate. The unreacted area surrounding the reaction circle serves as a negative internal control and a reference for comparing signal intensity.
9. Repeat step 7, washing test surface. Close the test device at the corners and leave for 10–15 seconds. Open and examine for colour change.

Interpretation of results

Upon completion of each test the test surface must be examined under a bright light. The light must be reflected off the test surface to observe the test results. A positive internal control dot is present on each test surface; it appears as a small blue/purple dot in the centre of the test surface upon completion of the test. A negative test result will show only the positive internal control dot. A positive test result will show the positive internal control dot within the reaction circle. With very strong positive results the positive internal control dot may be less apparent within the reaction circle.

Positive or weak positive result

Filled-in blue/purple coloured reaction circle of any intensity appears in the centre of the test device.

Negative result

No filled-in blue/purple reaction circle of any intensity appears on the test surface. The positive control dot appears in the centre of the test surface. The appearance of a ring effect with no internal shading must not be interpreted as positive.

Invalid result

No blue/purple positive internal control dot or a solid blue/purple colour over the entire test device surface. If an invalid result is obtained, then the entire test must be repeated, following the instructions carefully. If a second invalid result is obtained, then the results cannot be reported and the research biomedical scientist must be made aware of the problem.

Precautions and hazards

- Reagent 1A is a corrosive (sodium hypochlorite, < 15% available chlorine). Avoid contact with skin, eyes and mucous membranes. If reagent comes into contact with these areas, then wash with copious amounts of water.
- Reagent 1B is a corrosive (0.5 M acetic acid, pH3). Avoid contact with eyes and mucous membranes. If the reagent comes into contact with these areas, wash with copious amounts of water.
- The extraction tubes contain 94% sodium nitrite, which is a toxic/irritant.
- Care must be taken not to touch the test surface or subject it to abrasion. This may cause damage to the test area resulting in altered test interpretation.

General laboratory precautions

- All patient specimens must be handled as though they are capable of causing infection. Follow basic laboratory safety guidelines.
- Never interchange reagents between kits.
- Do not interchange caps between reagents.
- Use a new transfer pipette or pipette tip for each specimen, reagent or test.
- The assay must be performed within the time ranges recommended, otherwise invalid results may occur.
- A laboratory coat and disposable gloves should be worn whilst handling the kit and specimens.
- Do not drink or eat in the laboratory area.
- Dispose of the reaction tubes and any other used reagents, etc., in a suitable container.
- Wash hands after performing the tests.

Appendix 2

Implementation of point-of-care testing

Point-of-care (POC) testing is currently one of the most active segments in the laboratory diagnostics industry.¹³⁹ However, it has so far had limited impact on microbiological diagnosis. To a large extent this has been because of the lack of test kits that offer both clinically useful sensitivity and specificity and practically as POC tests. Recent technological advances have facilitated the development of new microbiological diagnostic methods that allow rapid and accurate diagnosis and which might therefore be suitable for POC use.

There are no international standards around the suitability of the use of tests at the POC level. In the USA diagnostic testing is regulated by the Food and Drug Administration, which categorises tests as waived or of moderate or high complexity.¹⁴⁰ Waived tests are defined as non-critical tests that do not require regulatory oversight because they employ methodologies that are so simple and accurate that the likelihood of an erroneous result is minimal and/or they are deemed to present no reasonable risk of harm to the patient if the test is performed incorrectly. Waived tests account for the vast majority of POC testing in the USA.¹⁴¹ However, only a limited number of microbiological diagnoses can be made using waived tests because, in general, simplicity of microbiological tests is achieved only at the expense of accuracy. Guidance on POC testing in the UK has been produced by a number of bodies, including the Medicines and Healthcare Products Regulatory Agency (MHRA),¹⁴² the Royal College of Pathologists¹⁴³ and the Institute of Biomedical Science.¹⁴⁴ None of these guidelines makes specific recommendations in relation to the complexity of POC tests; however, they all emphasise the importance of staff training and competency assessment.

This study investigated the POC use of two commercially available diagnostic kits for GBS. One was an OIA (BioStarOIA STREP B®) and the other a PCR system (Smart GBS® kit and SmartCycler® system). These tests are categorised by the US Food and Drug Administration as being of moderate and high complexity respectively. The implementation of these tests at the POC level was carefully planned, taking account of standards and recommendations set by the UK MHRA and other UK and international agencies.

Staff selection

We elected to make midwifery assistants responsible for testing. These are unqualified staff, with little or no scientific background, who support the day-to-day running of the delivery suite. This staff group was chosen because it was considered that midwifery assistants would be more readily available to undertake testing on demand, as well as to minimise the salary component of the overall cost of tests, which require considerable hands-on time. Moreover, some midwifery assistants were already undertaking POC tests for haemoglobin and plasma glucose concentrations.

Training needs analysis

Because of the complexity of the tests being evaluated and the special infection control considerations involved in microbiological testing, a full training needs analysis was undertaken. This identified a number of basic elements of laboratory practice in which it was considered essential that midwifery assistants achieved competence before receiving any hands-on training with the diagnostic kits. These areas were general good laboratory practice, health and safety and quality assurance. The results generated from the rapid tests used in this study were not used to influence patient management and therefore comprehensive training on the interpretation of results generated by the POC tests was not given. However, the training needs analysis identified that those undertaking testing would have to understand the importance of generating timely and accurate results and be competent in identifying patterns of results that might indicate a problem with testing.

Training and competency assessment

A series of three seminars was provided for midwifery assistants to introduce them to the study and to provide training on the basic elements of laboratory practice outlined above. Training was provided by a biomedical scientist. Each seminar lasted approximately 45 minutes and consisted of an informal presentation with discussion allowed around each point made during the presentation. At the end of each seminar each midwifery assistant was given a questionnaire designed to assess the

level of understanding and to highlight areas of uncertainty. When difficulties were identified these were dealt with discreetly by further tuition on a one-to-one basis.

Only when we were satisfied that individuals had demonstrated basic competency were they allowed to progress to hands-on training in the use of the kits. Individuals conducted the tests under the supervision of the biomedical scientist, as many times as necessary, until they felt comfortable in what they were doing and the assessor was satisfied that they could achieve a satisfactory and consistent level of competency.

Feedback

Midwifery assistants were given feedback questionnaires in which they were asked their opinions on the quality of the seminars and their overall views of the study. They were free to make any suggestions on how they thought that training could be improved. Finally, it was made clear that they could telephone either the biomedical scientist or the research midwife at any point during the study if there was a problem.

Ongoing competency and quality assurance

Each participating midwifery assistant was regularly asked if any issues or problems had arisen. Results were regularly monitored by the biomedical scientist to establish if there were any patterns of invalid results or test failures occurring. The PCR kit has its own integral controls that have to be incorporated with each run; if either, or both, of these are invalid then the whole run is invalidated. The OIA kit contained internal controls that were used with each batch.

Results

In total, 12 midwifery assistants were trained in POC testing. All easily attained competency in the basic elements of laboratory practice. Responses in the feedback questionnaires also indicated that they were happy with the method of training and that they felt confident and enthusiastic about the study and their new role in POC testing.

All midwifery assistants readily become competent and confident at undertaking the OIA test after an average of 2 hours of hands-on training. The only aspect to cause concern was the reading of the final result, which was open to a degree of subjective interpretation. Trained midwifery

assistants were able to process a swab and achieve a result within 35 minutes, with 20 minutes of actual hands-on time. The PCR test, which entails over 20 separate manipulations during sample preparation, proved more daunting and, although all midwifery assistants achieved competency after the initial training, few had sufficient confidence to feel comfortable about testing. Training also took much longer than for the OIA test, averaging 7 hours per midwifery assistant. It took an average of 90 minutes to obtain a PCR result, including 40 minutes hands-on time. An unanticipated problem that arose during the study, related to the complexity of sample preparation for both tests, meant that staff were unable to begin processing a further sample until they had completed work on the first sample.

At no time during the study were we able to establish testing on demand on a 24/7 basis. In the early stages of the study, midwifery assistants were available to undertake POC testing during daytime hours, 7 days per week. However, over a period of time, fewer tests were being performed in real time by fewer midwifery assistants. There were several reasons for this, with the main ones being the impossibility of maintaining adequate levels of fully trained staff because of high staff turnover, compounded by delays in recruiting replacements, and the fact that midwifery assistants were often called away to undertake other duties for which they were responsible as part of their daily work schedule. Over the course of the study many midwifery assistants became disenchanted with the study as they saw it as extra work with no extra reward and they found it was easier to leave the swabs for the research staff to complete.

Discussion

A US survey¹⁴⁵ showed that nurses and midwives were the commonest staff group undertaking POC testing (46%), followed by medical assistants (25%) and physicians (9%). For the complex tests used in this study we did not consider that it was feasible to employ midwives to perform tests that would take them away from patient care for over 1 hour per test. We found that it was possible to train midwifery assistants to conduct the POC tests, although initial and ongoing training required a significant time commitment on the part of midwifery assistants and the trainer. However, with the resources available to us we encountered unexpected practical difficulties in delivering results within a clinically useful time frame and throughout the day and night. Staff shortages, created by vacancy management and

used as a component of financial recovery plans, are common in NHS hospitals and we did not appreciate beforehand the impact that this could have on the viability of a POC testing programme requiring a significant amount of labour. A survey¹⁴⁵ of US sites undertaking POC testing highlighted the difficulties in maintaining adequate staffing even for simple waived tests. The impact of staff shortages in our study would probably have been less had the testing requirement been limited to a single test of moderate complexity.

We do believe that, in principle, both the OIA and PCR tests are feasible at the POC level; however, to

achieve the degree of reliability in the generation of timely results that would be required to underpin a screening programme a very significant additional staff resource would be required, especially for the PCR test. Moreover, because of the complexity of sample preparation we consider that testing would have to be undertaken at defined times (e.g. hourly or 2-hourly) rather than strictly on demand. This would have an impact on the proportion of tests that deliver results sufficiently early in labour to enable adequate IAP to be provided to colonised mothers.

Appendix 3

Data completeness and neonatal outcomes

Data were available for the OIA and PCR tests from at least 77% and 99% of collected swabs, respectively, as shown in *Table 33*. There are fewer OIA test results than PCR test results as the manufacturer of the OIA kit was unable to maintain a constant supply to the study in the later months. When there were kit shortages, testing vaginal swabs was prioritised over testing rectal swabs. Swabs from the King George Hospital were sent to Birmingham Women's Hospital for the PCR test as a PCR thermocycler was not installed at the Essex site. Some tests were not performed because the swabs were too old by the time that they were received at Birmingham.

Virtually all of the OIA tests performed gave a result, suggesting that the test is capable of being used by midwifery staff and can reliably deliver a result. Approximately 1% of PCR tests failed, although this figure may be an underestimate as

midwifery staff may not have recorded any initial attempts that were successfully repeated.

Table 34 shows the number of pairs of test results for which both results are available for the various rapid test–reference test combinations and as a percentage of the potential total number of swabs collected.

Neonatal outcomes and adverse events

In total, 15 babies were reported to have had an infection immediately postpartum, of which six were invasive. Of the invasive infections three were diagnosed as EOGBS disease; all of these babies recovered. Four babies with infection were not given antibiotics, three of whom had superficial infection only. The fourth died from hypoxia and infection, although the cause of the infection

TABLE 33 Completeness of rapid test data

Test status	Vaginal			Rectal			Baby
	OIA	PCR	Reference test	OIA	PCR	Reference test	Reference test
Consented	1400			1400			
Collected	1394	1399	1398	1394	1398	1398	1291
Performed	1202	1379	1394	1079	1378	1393	1289
Result obtained	1197	1357	1387	1074	1357	1385	1281
Test failure	0	17	0	0	14	0	0
Inconclusive	0	0	0	0	2	0	0
No data	5	5	7	5	5	8	8

OIA, optical immunoassay; PCR, polymerase chain reaction.

TABLE 34 Swab pair completeness by reference standard

	Maternal reference		Baby reference	
	OIA	PCR	OIA	PCR
Vaginal ^a	1191 (85%)	1352 (97%)	1104 (86%)	1251 (97%)
Rectal ^a	1069 (77%)	1352 (97%)	987 (77%)	1250 (97%)
Either vaginal or rectal	1068	1340		

OIA, optical immunoassay; PCR, polymerase chain reaction.
 a Percentages in brackets refer to number of complete test pair results as a percentage of total reference results available.

is unknown as the postmortem was performed elsewhere. Four babies died from other causes.

In total, 82 babies were given antibiotics within 7 days of delivery. Of these, nine had an infection,

eight had no information about infection and the remaining 65 received antibiotics prophylactically.

There were no adverse events associated with taking the swabs, the testing procedure or the administration of antibiotics to the mother or baby.

Appendix 4

STARD checklist for the reporting of studies of diagnostic accuracy

Section and topic	Item		Page
Title/abstract/keywords	1	Identify the article as a study of diagnostic accuracy	ix, x
Introduction	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups	9,10
Methods			
Participants	3	Describe the study population: the inclusion and exclusion criteria, setting and locations where the data were collected	11
	4	Describe participant recruitment: was recruitment based on presenting symptoms, results from previous tests or the fact that the participants had received the index tests or the reference standard?	11
	5	Describe participant sampling: was the study population a consecutive series of participants defined by the selection criteria in items 3 and 4? If not, specify how participants were further selected	11 (consecutive series)
	6	Describe data collection: was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	11 (prospective)
Test methods	7	Describe the reference standard and its rationale	
	8	Describe technical specifications of material and methods involved, including how and when measurements were taken, and/or cite references for index tests and reference standard	
	9	Describe definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard	12 (cut-off n/a)
	10	Describe the number, training and expertise of the persons executing and reading the index tests and the reference standard	89
	11	Describe whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers	12 (masked)
Statistical methods	12	Describe methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals)	13
	13	Describe methods for calculating test reproducibility, if carried out	n/a
Results			
Participants	14	Report when study was carried out, including beginning and ending dates of recruitment	13
	15	Report clinical and demographic characteristics of the study population (e.g. age, sex, spectrum of presenting symptoms, comorbidity, current treatments, recruitment centres)	15

continued

Section and topic	Item		Page
Test results	16	Report the number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to receive either test (a flow diagram is strongly recommended)	14
	17	Report time interval from the index tests to the reference standard, and any treatment administered between	Index and reference test samples collected simultaneously
	18	Report distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition	16
	19	Report a cross-tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, report the distribution of the test results by the results of the reference standard	17,93
Estimates	20	Report any adverse events from performing the index tests or the reference standard	94
	21	Report estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals)	17
	22	Report how indeterminate results, missing responses and outliers of the index tests were handled	93
	23	Report estimates of variability of diagnostic accuracy between subgroups of participants, readers or centres, if carried out	38
Discussion	24	Report estimates of test reproducibility, if carried out	Not done
	25	Discuss the clinical applicability of the study findings	19–22

n/a, not applicable.
First official version, January 2003.

Appendix 5

Independent monitoring of test accuracy studies

Background

The NIHR Health Technology Assessment (HTA) programme funded this project on the accuracy and cost-effectiveness of the rapid diagnosis of group B streptococcus during labour (project number 02/38/04) in October 2004. The issue of independent monitoring of the test accuracy study within this project was raised at the outset. The HTA programme had commissioned few primary test accuracy studies previously, but the requirements for independently monitoring these types of study had not necessarily been considered to be distinct from existing guidance on independent monitoring of RCTs. The investigators took it upon themselves to develop a model for independent monitoring that would provide external input and supervision throughout the course of their study, which was accepted by the HTA programme. Based on our experience we report some recommendations for the monitoring of test accuracy studies.

Preamble

All clinical research that involves the prospective study of patients needs some form of independent monitoring.¹⁴⁶ In the UK, public funders of research, including the HTA programme and the Medical Research Council, require independent monitoring committees to be established for all RCTs,^{147,148} although the approach employed in the UK may not be the model used elsewhere.¹⁴⁹ In RCTs of effects of interventions, an independent trial steering committee (TSC) oversees the management and financial aspects of the study, and a data monitoring committee (DMC) (also sometimes known as a data monitoring and ethics committee or a data monitoring and safety board) oversees the accumulating data. There is no legal requirement by regulatory authorities for RCTs to convene DMCs, although guidance exists from the US Food and Drug Administration as to when and how they should be employed.¹⁵⁰

The TSC and DMC are each composed of a small number of individuals who have pertinent expertise and are independent of the study investigators and host institutions, generally having no role in

the initial design or conduct of the study. Their primary role is to provide overall supervision of the study, to ensure that the study is conducted to good research standards, to scrutinise interim data and to advise the sponsor regarding the continuing integrity of the study and the safety of current and potential future participants in the trial. By having access to the accruing data, the DMC is able to make an objective assessment as to whether the primary research question has been answered. In the process, the TSC and DMC also play a valuable role in overseeing protocol compliance and study validity so that reliable and objective evidence is produced. There have been numerous recommendations regarding the establishment and operation of DMCs for RCTs, most notably the UK DAMOCLES project.¹⁵¹ Following a comprehensive review of the literature¹⁵¹ this project provided detailed guidance on the conduct of DMCs. Other groups, including the Society for Clinical Trials, have considered monitoring arrangements for trials that typically have not employed DMCs, including early phase exploratory trials.¹⁵² Unfortunately, none of these provide guidance as to how and when independent monitoring should be employed in primary test accuracy studies.

Here we propose guidance for monitoring test accuracy studies, detailing the main issues to be considered and providing operational guidance for investigators and independent monitoring committee members. Our objective is to encourage researchers and sponsors currently engaged in diagnostic research to consider employing external monitoring of accuracy studies, and to initiate a discussion about formalising the independent monitoring of such research in the future.

Study design considerations for independent monitoring

In the evaluation of tests there are many possible designs.^{81,153} The fundamental difference between test accuracy studies and RCTs of effectiveness of interventions is that, in the former, randomisation to difference tests is generally not necessary; typically all participants suspected of having the target condition are subject to both the test

of interest (index test) and a confirmatory test or observation (reference standard). The aim, therefore, is to determine the consistency of the index test relative to the reference standard (as in Chapter 2). Accuracy is described in terms of sensitivity and specificity of the index test, amongst other parameters. Inevitably test accuracy studies will vary in complexity depending on the numbers and types of index tests and reference standards, the numbers and types of participants and centres, the need to embed these within an HTA, etc. Our guidance largely relates to relatively large studies conducted over a period of time such that monitoring will influence their ongoing progress.

In RCTs comparing the effectiveness of interventions, the benefits and harms of which are unknown, there is an over-riding concern about safety and stopping rules that underpins the desire to have independent monitoring. Usually, DMCs for RCTs review accruing data in confidence and make a recommendation on whether to stop the trial, continue recruiting or modify the trial protocol. The DMC may prespecify criteria or thresholds of difference between the treatment groups, with important and statistically significant differences dictating closure of the trial.^{154,155} Any DMC recommendation is considered by the TSC, which makes a decision on behalf of the sponsor, based on the DMC's recommendation and other external evidence and circumstances. The TSC does not have access to the interim data seen by the DMC, allowing them to make objective decisions without being influenced by the emerging results. *Figure 18a* demonstrates the relationship between various committees in a typical RCT of interventions.

Can the same data monitoring model be applied to primary test accuracy studies? There are some important considerations that may require the model to be adapted. These centre around the need for confidential assessment by the independent monitors, the relationship that the DMC has with the TSC and the criteria used to decide whether to recommend halting the study. Difficulties arise in the area of stopping criteria, in which there is virtually no work, and in the area of confidentiality of the interim data. The question to ask is whether access to the interim data would influence the decision of the monitors regarding study continuation. If it is considered likely that it might, as is often the case in RCTs of interventions, then the TSC and DMC should be established to function separately. This guidance does not seek to dictate when analyses should be kept confidential

or not. The consequences for each study should be assessed before the start and the most appropriate model of monitoring employed depending on the perceived risks to the study.

In general, it can be argued that the observational design of test accuracy studies does not require the same levels of independence as those employed in RCTs. In test accuracy studies the main concern is harm to participants from the tests, which might also affect the completeness of verification. Another consideration is whether clinical behaviour might be influenced by early release of interim results, leading to early adoption of the test or loss of the opportunity to verify the index test by the reference standard. If so, the monitors should review the accuracy data in confidence. However, when it is unlikely that access to accuracy data will influence the decision-making processes there is the potential for a single entity to monitor data and oversee the study, or for the independent members of the monitoring committee to be convened as a subcommittee for data monitoring (*Figure 18b*). This would facilitate easy decision-making and avoid duplication of effort, simplifying the monitoring process. Further work to guide study investigators and, in particular, the development of criteria for stopping test accuracy studies is needed.

Aspects for consideration by independent monitors

Independent monitoring should consider the rate of recruitment, the disease prevalence, study quality, accuracy estimates, safety and the need for additional analyses. We believe that most of this information, except for accuracy estimates, can always be shared openly.

Recruitment

Recruitment rates should be monitored against predetermined targets, projected on the basis of the assumed prevalence and target sample size. When the rate of recruitment of patients in the study is lower than anticipated the monitors should take into account the reasons for the reduced participation. An extension of the duration of the study may be required to help estimate accuracy with adequate power, particularly sensitivity in conditions of low prevalence. Variation in accuracy in prespecified subgroups will not be reliably assessed if the study does not recruit to the original sample size, and spectrum bias could arise. If the recruitment rates are slow because of patient or physician dissatisfaction with the study, the monitors should consider whether to close

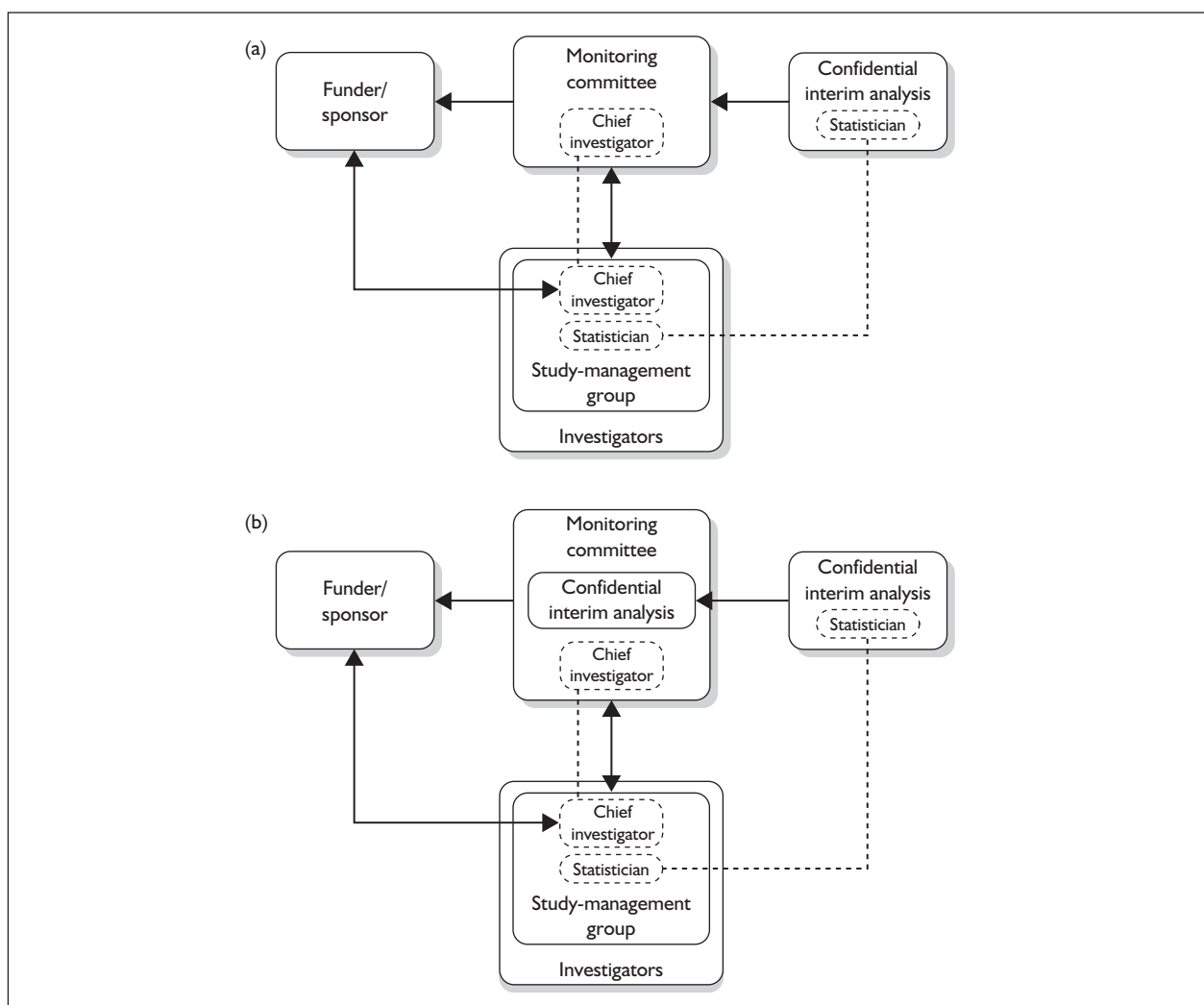


FIGURE 18 Independent monitoring of randomised controlled trials of effects of interventions and of test accuracy studies. (a) Model for independent monitoring of randomised controlled trials. (b) Model for independent monitoring of test accuracy studies.

recruitment to all patients or a specific subgroup or spectrum of patients because of futility. In this situation the recommendation to stop early may be aided by external valid and reliable evidence (systematic review or large primary study) on the accuracy of the index test(s).

Prevalence and spectrum

Analysis of the interim data may refute or substantiate the initial assumptions made about the disease prevalence rate in the study protocol. The precision of estimates of sensitivity depends entirely on the absolute number of abnormal cases. Therefore if disease prevalence is lower than anticipated, a larger sample will need to be recruited, perhaps over an extended period of time. Unexpected variations in the prevalence of the condition can have dramatic effects on the required sample size. A restricted disease spectrum in the sample could introduce spectrum bias¹⁵⁶

and may also have implications for sample size depending on the a priori assumptions about disease prevalence and accuracy amongst specific spectra. Analysis of test accuracy in predefined subgroups enables differential accuracy in different spectra to be detected and, if necessary, recommendations to be made for specific groups.

Study quality

It is the role of the investigators to ensure that the protocol is adhered to during the course of the study, but violations may be apparent only through detailed checking of the data. If there are any deviations from the original protocol, the reasons for these and their impact on the internal and external validity of the study are to be fully assessed. Interim data may allow an insight into compliance with items of study quality that relate to the study's conduct (Table 35).¹⁰⁰ For example, if a number of patients do not have their index

test results verified by a reference standard, this will lead to partial verification, which may have a biasing effect on the accuracy estimates.¹⁵⁷ Also, if clinicians become aware of index test(s) results during the course of the research, use of an effective treatment for test-positive cases could influence the reference standard, and the index test(s) may erroneously turn out to be less accurate (treatment paradox).^{158,159} Monitoring these issues will identify study deficiencies that need to be addressed by the investigators.

Accuracy estimates of index test(s)

The various parameters of test accuracy, including sensitivity, specificity, predictive values and likelihood ratios, should be estimated, with confidence intervals. The monitors may wish to examine accuracy estimates in clinically important disease subgroups too. The power to detect heterogeneity in accuracy between subgroups at interim analyses may be limited because of small sample size, but the likelihood of such heterogeneity will alert the monitors to the possibility of spectrum bias in the completed study.¹⁵⁶ Any deviations from assumptions made initially should be noted and the original sample size and power estimations revised if necessary. These have been reported only rarely in the previous test accuracy literature.⁹ It is essential in test accuracy studies to have sufficient power to estimate accuracy with sufficient precision. Sample sizes for test accuracy studies are calculated in various ways,^{10,11} but require an estimate of the prevalence of the target condition and a lower limit for sensitivity and/or specificity at which the index test is sufficiently precise. In coming to a decision about the lower limit of acceptable accuracy the investigators should have given consideration to the consequences of both false-positive and false-negative cases, and the lower limit of the 95% confidence interval of the test should not fall

below that limit. The monitors should consider the assumptions made in the sample size calculation and, at any interim analysis, decide whether the confidence intervals of the accuracy parameters are sufficiently precise.

Safety

The safety of the patients should not be compromised, either by the test(s) or the reference standard(s) performed. The protocol development process would have considered the risk of adverse events from the test(s) and the reference standard(s), and the background risk of the method of obtaining the test sample material, for example by venepuncture or colonoscopy. All attempts to minimise hazards associated with the tests should have been considered by the chief investigator and approved by a research ethics committee. Monitoring adverse events should lead to consideration of either stopping the study or introducing modifications in the execution of the test(s) or reference standard(s) if any hypothetical risks materialise during the course of the study. If the resultant protocol modifications lead to inadequacies in the verification of the presence or absence of disease, the imperfections in the reference standard may invalidate the accuracy estimates obtained from the study.^{157,160}

Additional data analysis

The independent monitors may suggest additional data analyses not planned at the protocol stage based on the interim results or recent external evidence. It is essential that the validity of this external evidence is appraised before any recommendations are made. Specialised statistical techniques might be helpful in partial/differential verification designs.^{161–163} It may be necessary to perform multivariate analysis,^{164,165} considering other variables that may affect the accuracy of the index test or use of different thresholds to assess

TABLE 35 Monitoring study quality (validity) in a test accuracy study

Key study quality items	Assessment at protocol stage	Assessment at interim analysis
Appropriate methods for patient recruitment and composition of spectrum	×	×
Appropriate reference standard(s)	×	
Independence of the index test(s) from reference standard(s)	×	
Blinding of assessors to the results of index test(s) or reference standard(s) or both, as appropriate	×	×
Completeness of verification of the results of index test(s) by reference standard(s)	×	×
Standardisation of both index test(s) and reference standard(s) between investigators and quality control measures		×

the accuracy of the test. The performance of the test may have to be considered separately across various subgroups that are clinically relevant in case of important spectrum variability.

Organisation and conduct of independent monitoring committees

Many of the useful recommendations on the practical aspects of independent monitoring of RCTs^{148,149,151} can be easily translated to the conduct of monitoring committees for test accuracy studies.

Establishment of the independent monitoring committee

The study investigators should establish a study management group led by the chief investigator. This group should be responsible for the organisation of the independent monitoring committee meetings. The study statistician should be charged with the preparation and distribution of the open and confidential sections of the monitoring report and should be designated to write the minutes of the meeting. A suggested template for the independent monitoring committee report is given in *Table 36*. Independent monitoring committee meetings should be held periodically throughout the recruitment period, the frequency determined by the duration of recruitment. Additional meetings can be called if circumstances dictate, for example in case the prevalence deviates substantially from that anticipated. Face-to-face meetings are always valuable, and in particular for the first meeting when the responsibilities and relationships are being clarified. Subsequent meetings should be face to face when possible; however, external pressures often mean that teleconferences are the only suitable method of meeting. Whatever the format, the organisation should facilitate prompt

decision-making while minimising the time commitment of the independent monitors.

Composition

Monitoring committees for test accuracy studies should be limited to a small number of members, ideally between three and five. Members should include at least one clinician practising in the clinical area and knowledgeable about the tests employed and a statistician with experience of diagnostic research methods. Additional members should reflect any other specialties involved in the study, although they may lack practical experience in test accuracy studies. A clinical epidemiologist with expertise in diagnostic methodology will be an essential committee member and should be requested to chair the committee. The study investigators should be represented by the chief investigator and the study statistician. When it is decided that analyses should be provided in confidence by the study statistician and discussion of the data should take place in a closed session, the chief investigator should only attend open sessions. It would be appropriate for all members to declare any conflicts of interest that they may have, either in terms of academic interaction with other study personnel or in relation to the manufacturers of the tests under study or their competitors. Independent monitors should be reimbursed for expenses incurred but any additional payment should be agreed with the sponsor and ethics committee and declared at publication of the results.

Relationships

In RCTs, in which the DMC and the TSC are two separate entities, the DMC reports to the TSC, which makes recommendations on behalf of the sponsor. The same responsibilities apply to monitoring committees in a test accuracy study if it is agreed that interim data remain confidential, as

TABLE 36 Suggested composition of the monitoring report for a test accuracy study

Non-confidential interim analyses	Confidential interim analyses
Participant demographics	Test accuracy (sensitivity, specificity, likelihood ratios) – total and by subgroup
Recruitment rates	
Prevalence (defined by reference standard) – total and by subgroup	
Index test verification by reference standard	
Adverse events (all, whether considered related to test or not)	
External evidence from other studies and systematic reviews	

already discussed. Investigators and practitioners should not have access to interim accuracy results so that there is no premature influence on their conduct or clinical practice. As discussed before, when it is considered acceptable for the TSC to have access to interim accuracy data, a DMC that is made up of independent members of a larger TSC could be employed, as shown in *Figure 18b*.

Decision-making

The manner in which the DMC comes to make its recommendations about the continuing conduct of the study should be discussed and agreed early, soon after the protocol has been reviewed and endorsed. A suggested list of recommendations that could be made in a test accuracy study is provided in *Table 37*. Ideally a decision should be reached by consensus, and prespecifying the relative importance of the criteria under consideration would facilitate this. When the DMC will have a role in the TSC, the implications for the study (e.g. ethical, statistical, practical, financial) arising from any recommendation should be considered. It is the role of the TSC to initiate further actions to be taken as a result of the DMC recommendations, such as updating a systematic review with the accumulated data, performing individual patient data meta-analysis for specific subgroups or recalculation of the sample size, before any final decision is made.

After the study finishes

When a test accuracy study has finished recruiting, the independent monitors may play a role in the interpretation of the results and may comment on the draft of the manuscript prepared for publication of the study, ensuring that manuscripts are STARD compliant.⁷⁹ The DMC may also play a role in assuring that the evidence produced is not overstated, although this could be considered controversial in some circumstances. The membership and role of the DMC and the frequency of its meetings should be reported in the publication, as a matter of courtesy and to promote the use of DMCs in test accuracy studies. When the DMC forms a subgroup of the TSC, the relationship and decision-making process should be described. It should be agreed for how long after the study reports that independent monitors should refrain from discussing data and the decisions made.

Conclusion

Monitoring should be considered in all primary test accuracy studies. The specific role of independent monitors in test accuracy studies differs from their role in RCTs, although no formal recommendations pertaining specifically to independent monitoring in test accuracy studies exist. The monitors should ensure that the aim of the study to be undertaken is explicit from the outset and that the design chosen and

TABLE 37 Possible recommendations that could be made by a data monitoring committee in a test accuracy study

Recommendation	Rationale
No action	If the study is progressing according to the protocol and recruitment projections, the disease prevalence is as anticipated and no reason is seen not to continue recruitment to the planned sample size
The study should be closed immediately and completely	When there is proof beyond reasonable doubt on the following grounds: index test or reference standard has clearly been demonstrated to be harmful to the patient; convincing external evidence has arisen that reliably demonstrates that the test is highly accurate and of benefit to the whole spectrum of the population to whom it will be offered
The study should be closed to a particular subgroup on the grounds of safety or accuracy	For example when there is proof beyond reasonable doubt on the following grounds: index test or reference standard has clearly been demonstrated to be harmful to a particular subgroup; convincing external evidence has arisen that reliably demonstrates that the test is highly accurate and of benefit to the subgroup to whom it should be offered
The study should be closed because of futility	On the following grounds: reference standard is not, or rarely, completed as it is unavailable or unacceptable to study participants or clinicians; recruitment to the study is significantly behind schedule and, despite concerted efforts, the study is unlikely to meet its projected target sample size
The study should be modified	For example on the following grounds: amendment to the sample size based on the observed prevalence or accuracy; modification of the reference standard to improve verification of the presence or absence of disease

power estimations made are cognate with the aim. They should ensure that the disease prevalence and spectrum are monitored along with study quality, compliance with the protocol, safety and recruitment rates. Interim test accuracy estimates should be examined confidentially by independent monitors if there is a potential for clinical practice to be influenced by knowledge of interim results. Further work is required to establish the role of statistical stopping rules in the monitoring of test accuracy studies.

Contributors to this appendix

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Appendix 6

Model inputs for the cost-effectiveness evaluation

Prevalence and relative risks

The following neonatal prevalence calculations are based on *Tables 38* and *39*.

Relative risk (RR; treated versus untreated)

Maternal colonisation

$$\text{Vaginal delivery (RR}_{\text{vaginal}}) = a/b = 0.2250/0.4630 = 0.4860$$

$$\text{Caesarean delivery (RR}_{\text{caesarean}}) = c/d = 0.1333/0.2281 = 0.5843$$

$$\text{Overall RR} = [(n_{\text{vaginal}} \times \text{RR}_{\text{vaginal}}) + (n_{\text{caesarean}} \times \text{RR}_{\text{caesarean}})] / (n_{\text{vaginal}} + n_{\text{caesarean}}) = [(202 \times 0.4860) + (72 \times 0.5843)] / (202 + 72) = 140.2416/274 = 0.5118$$

No maternal colonisation

We could not calculate the RR for this group because of the zero values obtained for *e* and *g*. However, the expected number of positive cases for the treated group calculated using the overall RR from maternal colonisation above were:

$$\text{Vaginal delivery: } (75 \times 0.0110) \times 0.5118 = 0.4222$$

$$\text{Caesarean delivery: } (34 \times 0.0061) \times 0.5118 = 0.1061$$

These are both below 0.5 and therefore consistent with the observed number of positive cases for this group (i.e. zero for both). We have therefore assumed that it is reasonable to use the same overall RR for no maternal colonisation as for maternal colonisation (0.5118).

Prevalence

Maternal colonisation

$$\text{Vaginal delivery} = [(9/\text{RR}_{\text{vaginal}}) + 75]/n_{\text{vaginal}} = [(9/0.4860) + 75]/202 = 93.5185/202 = 0.4630$$

$$\text{Caesarean delivery} = [(2/\text{RR}_{\text{caesarean}}) + 13]/n_{\text{caesarean}} = [(2/0.5843) + 13]/72 = 16.4229/72 = 0.2281$$

No maternal colonisation

$$\text{Vaginal delivery} = [(0/\text{RR}_{\text{vaginal}}) + 8]/n_{\text{vaginal}} = (0 + 8)/795 = 0.0101$$

$$\text{Caesarean delivery} = [(0/\text{RR}_{\text{caesarean}}) + 1]/n_{\text{caesarean}} = (0 + 1)/197 = 0.0051$$

TABLE 38 Prevalence and relative risk of neonatal colonisation – definition

	Type of delivery	Number of positive baby test results/subtotal	
		Mother treated	Mother untreated
Maternal colonisation	Vaginal (n_{vaginal})	<i>a</i>	<i>b</i>
	Caesarean ($n_{\text{Caesarean}}$)	<i>c</i>	<i>d</i>
No maternal colonisation	Vaginal (n_{vaginal})	<i>e</i>	<i>f</i>
	Caesarean ($n_{\text{Caesarean}}$)	<i>g</i>	<i>h</i>

TABLE 39 Prevalence and relative risk of neonatal colonisation

	Type of delivery	Number of positive baby test results/subtotal	
		Mother treated	Mother untreated
Maternal colonisation	Vaginal ($n_{\text{vaginal}} = 202$)	9/40 = 0.2250	75/162 = 0.4630
	Caesarean ($n_{\text{Caesarean}} = 72$)	2/15 = 0.1333	13/57 = 0.2281
No maternal colonisation	Vaginal ($n_{\text{vaginal}} = 795$)	0/75 = 0.0000	8/728 = 0.0110
	Caesarean ($n_{\text{Caesarean}} = 197$)	0/34 = 0.0000	1/163 = 0.0061

Note: Total number of observations does not add up to 1400 because of missing data on numbers of mothers treated or untreated.

Time and motion study

A time and motion study was conducted to ascertain the time that it would take to conduct the PCR and OIA rapid tests (Tables 40–42). We followed an experienced biomedical scientist from the time that he received the maternal vaginal and rectal swabs from the maternity ward to the time that he produced a set of results after running the rapid tests. This was carried out on 3 and 2 non-consecutive days for the PCR and OIA tests respectively. Following the observation period the times that it took for each process were logged and the average of the three or two periods was calculated. It was assumed that it took on average 15 minutes for a midwife to collect swabs from a woman. This time was added to the total time taken for a test to be carried out. The steps

described in the instruction manuals for the PCR and OIA tests were adhered to.

Cost inputs

The cost of each test and each intervention was estimated from different sources, described in more detail below. All costs are presented in UK pounds and 2006 prices and are summarised in Table 43.

Costs of the tests

The costs for the tests (PCR, OIA and culture; Tables 44–46 respectively) were derived from two main sources: the Birmingham Women's Hospital (BWH) and the literature. The costs available from the BWH came from personal communication (Philip Milner, October and November 2006). The

TABLE 40 Polymerase chain reaction test

Activity/stage	Time (minutes)			
	Day 1	Day 2	Day 3	Average
(i) Collection of swabs (includes time for paperwork and sending swabs for processing)	15.00	15.00	15.00	15.00
(ii) Swabs placed into two sample buffers	5.00	5.00	5.00	5.00
(iii) Sample buffer placed on vortex	0.05	0.07	0.05	0.06
(iv) About 50 µl of each swab specimen transferred from buffer into lysis tube, after which buffer is discarded	0.17	0.15	0.17	0.16
(v) Lysis tubes placed on vortex	5.00	5.00	5.00	5.00
(vi) Lysis tubes centrifuged in microcentrifuge	0.25	0.25	0.25	0.25
(vii) Heat samples in lysis tubes on heating block at 95°C	2.00	2.00	2.20	2.10
(viii) Samples placed into ice bowl; put the following into the cooling block: (a) master mix for rectal or vaginal swab; (b) positive control; (c) negative control; add diluent to (a) master mix	10.00	9.00	8.00	9.00
(ix) Add lysate to master mix and centrifuge in microcentrifuge	0.17	0.17	0.17	0.17
(x) Mix master mix on vortex	0.17	0.17	0.17	0.17
(xi) Transfer master mix into thermocycler	42.00	42.00	43.00	42.33
Total	79.81	78.81	79.01	79.24

TABLE 41 Optical immunoassay test

Activity/stage	Time (minutes)		
	Day 1	Day 2	Average
(i) Collection of swabs (includes time for paperwork and sending swabs for processing)	15.00	15.00	15.00
(ii) Three drops of reagent 1A added to each extraction tube and mixed	3.25	3.30	3.28
(iii) Add reagent 1B and mix thoroughly	3.25	3.25	3.25
(iv) Add neutralising reagent 2	0.08	0.10	0.09
(v) Withdraw swab and add three drops of reagent 3	0.25	0.33	0.29
(vi) Mix using transfer pipette and wait	10.00	10.20	10.10
(vii) Transfer to reaction square	0.17	0.15	0.16
(viii) Pour wash solution and close	0.17	0.17	0.17
(ix) Add substrate and wash off to reveal result	5.25	5.00	5.12
Total	37.42	37.50	37.46

TABLE 42 Probability of test results being in time^a

Parameter	Value	Source
PCR		
Maternal colonisation and vaginal delivery	192/212 = 0.9060	GBS study
Maternal colonisation and Caesarean delivery	79/79 = 1	GBS study
No maternal colonisation and vaginal delivery	796/846 = 0.9409	GBS study
No maternal colonisation and Caesarean delivery	212/216 = 0.9810	GBS study
OIA		
Maternal colonisation and vaginal delivery	205/212 = 0.9670	GBS study
Maternal colonisation and Caesarean delivery	79/79 = 1	GBS study
No maternal colonisation and vaginal delivery	821 = 0.9700	GBS study
No maternal colonisation and Caesarean delivery	215/216 = 0.9950	GBS study
OIA, optical immunoassay; PCR, polymerase chain reaction.		
a Based on Table 40 (PCR) and Table 41 (OIA): for the PCR and OIA test results to be in time, the time between the collection of the swab and delivery of the baby should be ≥ 80 and ≥ 37 minutes respectively.		
Note: Total number of observations does not add up to 1400 because of missing data on test times.		

costs of the equipment used in all of the tests were obtained from the finance department purchase records of the BWH. As is standard practice¹⁶⁶ a lifespan of 5 years was assumed and all costs were discounted at 3.5%. Annual equipment costs were calculated and the equipment cost per test was determined by establishing the number of tests run in a year.

Unit costs for the materials used in the study were established from the BWH. The cost of material per test was calculated by dividing the unit cost for the material by the number of tests that could be run using each unit of materials.

Staff costs included training costs and the cost of the time spent conducting the test. The training of midwifery staff was carried out by a biomedical scientist within the team. On average, 7.5 hours was spent on training staff (BWH). The training cost per test (£0.14) was determined by first calculating the annual training costs to both midwifery staff and the biomedical scientist based on their salaries (NHS, 2007). The annual training cost (£294) was divided by the average number of tests that would be conducted in a year (2058 – BWH) to obtain the training cost per test. The total cost of conducting the PCR test (explanation, swabbing and delivery of results by midwives and carrying out of the test

TABLE 43 Costs per patient for early-onset group B streptococcus (EOGBS)

Cost item	Cost (£)	Source
Tests		
<i>PCR (vaginal or rectal)</i>		Table 44
Equipment	2.55	
Materials	18.24	
Staff	9.16	
Total	29.95	
<i>OIA (vaginal or rectal)</i>		Table 45
Equipment	0.01	
Materials	8.06	
Staff	8.02	
Total	16.09	
<i>Culture (mother)</i>		Table 46
Equipment	0.01	
Materials	2.60	
Staff	8.02	
Total	10.63	
Antibiotics		
		Table 47
<i>Penicillin</i>		
Materials	8.04	
Staff	6.45	
Total	14.49	
<i>Clindamycin</i>		Table 48
Materials	7.87	
Staff	4.30	
Total	12.17	
Cost of delivery		
Normal delivery	891.00	
Caesarean delivery	1643.00	
Cost of disease		
<i>Mother (cost of treatment)</i>		
Penicillin	14.49	Table 47
Clindamycin	12.17	Table 48
Weighted total	14.28	
<i>Baby</i>		
EOGBS – death	1537.91	Table 49
EOGBS – no death	534.25	
Cost of identifying risk factors		
		Table 50
Previous GBS-affected baby	0.43	
Intrapartum fever (> 38°C)	6.45	
Preterm labour	6.45	
GBS detected	10.17	
Prolonged rupture of membranes (> 18 hours)	0.43	
Weighted total	2.96	

TABLE 44 Costs for polymerase chain reaction (PCR) test

Cost item		Cost per test (£)	Source
Equipment ^a	Vortex	0.01	BWH
	Micropipettors		
	1–10 µl	0.07	BWH
	10–100 µl	0.06	BWH
	Microcentrifuge	0.01	BWH
	Dry heating block	0.03	BWH
	Stopwatch or timer	0.00	
	SmartCycler starter system: DX Software, processing block, user manual, accessory kit and desktop computer	2.25	BWH
	Fridge	0.01	BWH
	Stopwatch or timer	0.00	BWH
	Total	2.45	
	Total at 2005/6 prices	2.55	
Materials	Sample buffer, lysis tube, master mix, positive control, negative control, diluent, specimen identification labels	18.00	BWH
	Pipette tips (0.1–10 µl)	0.00	BWH
	Pipette tips (0–250 µl)	0.02	BWH
	Swab containers	0.12	BWH
	Swabs	0.04	BWH
	Powderless disposable gloves	0.06	BWH
	Ice or cooling block	0.00	BWH
	Total	18.24	
Staff	Training costs	0.14	BWH and GBS time and motion study;
	Conducting the test		Curtis and Netten 2006; ¹²¹
	Explanation and swabbing	3.23	NHS 2007 ^{128,129}
	Carrying out the test	2.56	
	Delivery of results	3.23	
Total	9.16		
Total cost for PCR		29.95	

BWH, Birmingham Women's Hospital.
a Costs for equipment discounted at 3.5%; lifespan assumed to be 5 years.

by biomedical scientists) was estimated at £9.02 per test whereas the total costs for conducting the OIA and culture tests were estimated at £7.88 because of the shorter time required to carry out these two tests.

Costs of IAP and treatment

Two drugs, clindamycin and penicillin, are recommended for GBS treatment as standard practice.⁶¹ The cost of administering these drugs was calculated using estimates from Curtis and Netten,¹²¹ the NHS,^{128,129} the *British National Formulary*¹⁶⁷ and the BWH (Tables 47 and 48). Staff costs included the cost of the time spent

setting up the intravenous equipment as well that for delivering the drug for a single dosage and subsequent dosages (for penicillin only). The cost of materials was also included. Because two dosages were needed for treatment with penicillin, the cost per patient of administering it was much higher than that for clindamycin. A weighted total cost of £14.28 for both antibiotics was used for all calculations (Table 49).

Cost of EOGBS

The costs of EOGBS for the mother and for the baby were calculated separately (Table 49). The cost for the mother was made up of the costs of delivery

TABLE 45 Costs for optical immunoassay (OIA) test

Cost item		Cost per test (£)	Source
Equipment ^a	Fridge	0.01	BWH
	Stopwatch or timer	0.00	
	Total	0.01	
Test-specific equipment	Test devices – 30 each		
	Extraction tubes – 30 each		
	Transfer pipettes – 30 each		
Materials	Reagent 1A – 3.8 ml		
	Reagent 1B – 3.8 ml		
	Reagent 2 – 3.6 ml		
	Reagent 3 – 3.6 ml		
	Reagent 4 – 125 ml		
	Substrate		
	Positive control – 0.7 ml		
	Swabs – 30 each		
	Total (test-specific equipment and materials)	8.06	BWH
	Staff	Training costs	0.14
Conducting the test			
Explanation and swabbing		3.23	
Carrying out the test		1.42	
Delivery of results		3.23	
	Total	8.02	
Total cost for OIA		16.09	

BWH, Birmingham Women's Hospital.
a Costs for equipment discounted at 3.5%, lifespan assumed to be 5 years.

TABLE 46 Costs for culture test (mother)

Cost item		Cost per test (£)	Source
Equipment ^a	Fridge	0.01	BWH
	Stopwatch or timer	0.00	
	Total	0.01	
Materials	Enrichment broth	0.90	BWH
	Agar plates	1.44	
	Swab	0.24	
	Gloves	0.02	
	Total	2.60	
Staff	Training costs	0.14	BWH and GBS time and motion study; Curtis and Netten 2006; ¹²¹ NHS 2007 ^{128,129}
	Conducting the test		
	Explanation and swabbing	3.23	
	Carrying out the test	1.42	
	Delivery of results	3.23	
	Total	8.02	
Total cost for culture		10.63	

BWH, Birmingham Women's Hospital.
a Costs for equipment discounted at 3.5%, lifespan assumed to be 5 years.

and treatment. The source of information for the costs of a normal and a Caesarean delivery was the UK HRG costs.¹²⁹ The cost of penicillin and clindamycin treatment was as calculated above. The costs of EOGBS death and non-fatal EOGBS for babies were obtained from Colbourn *et al.*⁶⁹

Cost of identifying risk factors

The cost of identifying risk factors was determined by ascertaining the time that midwives and junior doctors took to identify the risk factors (*Table 50*) and then calculating the cost based on their salaries. Only one risk factor (GBS detected) involved a medical secretary in reporting the findings of the culture test used to detect GBS. A weighted mean cost of £2.96 was calculated for identifying risk factors.

Discounting life-years

The life expectancy at birth in the UK is 76 years for men and 81 years for women (http://www.gad.gov.uk/Demography%20data/Life%20tables/Interim_life_tables.html). However, even at full health these estimates cannot be used as the true

yard stick for calculating an individual's stream of future health benefits as they do not take into account time preferences. A discounted life expectancy that incorporates these preferences would be a more accurate reflection. The recommended discount rate in the UK is 3.5%.¹²⁹

Table 51 shows the discounted survival curves that have been used to calculate the discounted life expectancy at full health. The first column (years) is the age of an individual and this has been capped at 100 years. The sum of the second and third columns (males and females, respectively) is the life expectancy at birth for an individual. This is shown to be 76 years for men and 81 years for women. Considering that a whole year is assumed for anyone who survives their first birthday, these values are an overestimate. The sum of the fifth and sixth columns (males discounted and females discounted) shows the discounted equivalent life at full health for men and women respectively. This means that the discounted equivalent life cannot be more than 27.0 years for men or 27.4 years for women.

TABLE 47 Costs for penicillin

Cost item		Cost per patient (£)	Source
Initial dosage			
Staff (midwife)	Setting up IV drip (5 minutes)	2.15	BWH; Curtis and Netten 2006 ¹²¹ ; NHS 2007 ^{128,129}
	Delivery (5 minutes)	2.15	
	Total	4.30	
Materials	Syringe	0.13	BWH; BNF 2007 ¹⁶⁷
	Needle	0.12	
	Saline for injection (20 ml)	1.04	
	Penicillin (3 g)	1.95	
	Cannula	2.53	
	Total	5.77	
	Subsequent dosage		
Staff (midwife)	Delivery (5 minutes)	2.15	BWH; Curtis and Netten 2006; ¹²¹ NHS 2007 ^{128,129}
Materials	Syringe	0.13	BNF 2007; ¹⁶⁷ BWH
	Needle	0.12	
	Diluent	0.00	
	Saline for injection	1.04	
	Penicillin (1.5g)	0.98	
	Total	2.27	
Total staff costs		6.45	
Total cost of materials		8.04	
Total cost		14.49	
BNF, <i>British National Formulary</i> ; BWH, Birmingham Women's Hospital; IV, intravenous.			

TABLE 48 Costs for clindamycin

Cost item		Cost per patient (£)	Source
Initial dosage			
Staff (midwife)	Setting up IV drip (5 minutes)	2.15	Curtis and Netten 2006 ¹²¹
	Delivery (5 minutes)	2.15	
	Total	4.30	
Materials	Syringe	0.13	BWH; BNF 2007 ¹⁶⁷
	Needle	0.12	
	Diluent	0.00	
	Saline for injection	1.04	
	Clindamycin (900mg)	4.05	
	Cannula	2.53	
	Total	7.87	
Total cost		12.17	
BNF, <i>British National Formulary</i> ; BWH, Birmingham Women's Hospital; IV, intravenous.			

TABLE 49 Costs of early-onset group B streptococcus (EOGBS)

Cost item		Cost per patient (£)	Source
Mother	Delivery		DoH 2006
	Normal	891.00	
	Caesarean	1643.00	
	Treatment		
	Penicillin	14.49	Table 47
	Clindamycin	12.17	Table 48
	Weighted cost	14.28	
Baby	EOGBS – death	1537.91	Colbourn <i>et al.</i> 2007 ⁶⁹
	EOGBS – no death	534.25	Colbourn <i>et al.</i> 2007 ⁶⁹

TABLE 50 Costs of identifying risk factors

Risk factor	Staff involved	Cost per patient (£)	Source
Previous GBS-affected baby			BWH; Curtis and Netten 2006; ¹²¹ NHS 2007; ^{128,129}
(1) Identification	Midwife (1 minute)	0.43	GBS time and motion study
Intrapartum fever (> 38°C)			
(1) Identification	Midwife (1 minute)	0.43	
Preterm labour			
(1) Identification	Junior doctor (10 minutes)	6.45	
GBS detected			
(1) Unenriched culture test			
Equipment		0.01	
Consumables		1.43	
Staff costs		8.02	
(2) Further reporting	Medical secretary (0.5 minutes)	0.13	
(3) Analysis of report	Junior doctor (0.5 minutes)	0.32	
(4) Report sent to GP	Medical secretary (1 minute)	0.25	
Total		10.17	
Prolonged rupture of membranes (> 18 hours)			
(1) Identification	Midwife	0.43	
Weighted mean		2.96	

TABLE 51 Discounting life-years

Years	Males	Females	Discount	Males discounted	Females discounted
0	1.0000	1.0000	1.0000	1.0000	1.0000
1	0.9940	0.9952	0.9662	0.9604	0.9615
2	0.9936	0.9948	0.9335	0.9275	0.9287
3	0.9933	0.9946	0.9019	0.8959	0.8971
4	0.9932	0.9945	0.8714	0.8655	0.8666
5	0.9930	0.9943	0.8420	0.8361	0.8372
6	0.9929	0.9942	0.8135	0.8077	0.8088
7	0.9928	0.9941	0.7860	0.7803	0.7814
8	0.9926	0.9940	0.7594	0.7538	0.7549
9	0.9925	0.9939	0.7337	0.7282	0.7293
10	0.9924	0.9938	0.7089	0.7035	0.7045
11	0.9923	0.9937	0.6849	0.6797	0.6806
12	0.9922	0.9936	0.6618	0.6566	0.6576
13	0.9920	0.9935	0.6394	0.6343	0.6353
14	0.9918	0.9934	0.6178	0.6127	0.6137
15	0.9916	0.9933	0.5969	0.5919	0.5929
16	0.9914	0.9931	0.5767	0.5717	0.5727
17	0.9910	0.9929	0.5572	0.5522	0.5533
18	0.9905	0.9927	0.5384	0.5332	0.5344
19	0.9898	0.9924	0.5202	0.5148	0.5162
20	0.9890	0.9921	0.5026	0.4970	0.4986
21	0.9882	0.9918	0.4856	0.4799	0.4816
22	0.9875	0.9915	0.4692	0.4633	0.4652
23	0.9867	0.9912	0.4533	0.4472	0.4493
24	0.9859	0.9909	0.4380	0.4318	0.4340
25	0.9851	0.9906	0.4231	0.4168	0.4192
26	0.9842	0.9903	0.4088	0.4024	0.4049
27	0.9835	0.9900	0.3950	0.3885	0.3910
28	0.9826	0.9896	0.3817	0.3750	0.3777
29	0.9817	0.9893	0.3687	0.3620	0.3648
30	0.9808	0.9889	0.3563	0.3494	0.3523
31	0.9799	0.9885	0.3442	0.3373	0.3403
32	0.9789	0.9880	0.3326	0.3256	0.3286
33	0.9779	0.9876	0.3213	0.3142	0.3173
34	0.9768	0.9870	0.3105	0.3033	0.3064
35	0.9757	0.9864	0.3000	0.2927	0.2959
36	0.9746	0.9858	0.2898	0.2825	0.2857
37	0.9734	0.9851	0.2800	0.2726	0.2759
38	0.9721	0.9844	0.2706	0.2630	0.2663
39	0.9708	0.9836	0.2614	0.2538	0.2571
40	0.9693	0.9827	0.2526	0.2448	0.2482
41	0.9677	0.9818	0.2440	0.2362	0.2396
42	0.9660	0.9807	0.2358	0.2278	0.2312

Years	Males	Females	Discount	Males discounted	Females discounted
43	0.9643	0.9795	0.2278	0.2197	0.2231
44	0.9623	0.9782	0.2201	0.2118	0.2153
45	0.9603	0.9768	0.2127	0.2042	0.2077
46	0.9579	0.9752	0.2055	0.1968	0.2004
47	0.9554	0.9734	0.1985	0.1897	0.1932
48	0.9524	0.9715	0.1918	0.1827	0.1863
49	0.9493	0.9694	0.1853	0.1759	0.1796
50	0.9458	0.9671	0.1791	0.1693	0.1732
51	0.9419	0.9645	0.1730	0.1630	0.1669
52	0.9379	0.9618	0.1671	0.1568	0.1608
53	0.9336	0.9588	0.1615	0.1508	0.1548
54	0.9290	0.9557	0.1560	0.1450	0.1491
55	0.9239	0.9521	0.1508	0.1393	0.1435
56	0.9183	0.9483	0.1457	0.1338	0.1381
57	0.9119	0.9440	0.1407	0.1283	0.1329
58	0.9050	0.9394	0.1360	0.1231	0.1277
59	0.8974	0.9345	0.1314	0.1179	0.1228
60	0.8889	0.9291	0.1269	0.1128	0.1179
61	0.8795	0.9231	0.1226	0.1079	0.1132
62	0.8693	0.9165	0.1185	0.1030	0.1086
63	0.8581	0.9095	0.1145	0.0982	0.1041
64	0.8462	0.9017	0.1106	0.0936	0.0997
65	0.8332	0.8932	0.1069	0.0891	0.0955
66	0.8190	0.8841	0.1033	0.0846	0.0913
67	0.8036	0.8739	0.0998	0.0802	0.0872
68	0.7867	0.8629	0.0964	0.0758	0.0832
69	0.7685	0.8508	0.0931	0.0716	0.0792
70	0.7485	0.8375	0.0900	0.0674	0.0754
71	0.7271	0.8230	0.0869	0.0632	0.0716
72	0.7036	0.8067	0.0840	0.0591	0.0678
73	0.6784	0.7889	0.0812	0.0551	0.0640
74	0.6515	0.7694	0.0784	0.0511	0.0603
75	0.6223	0.7481	0.0758	0.0471	0.0567
76	0.5916	0.7248	0.0732	0.0433	0.0531
77	0.5594	0.6997	0.0707	0.0396	0.0495
78	0.5259	0.6729	0.0683	0.0359	0.0460
79	0.4913	0.6445	0.0660	0.0324	0.0426
80	0.4558	0.6144	0.0638	0.0291	0.0392
81	0.4199	0.5823	0.0616	0.0259	0.0359
82	0.3840	0.5486	0.0596	0.0229	0.0327
83	0.3483	0.5130	0.0575	0.0200	0.0295
84	0.3124	0.4761	0.0556	0.0174	0.0265

continued

TABLE 51 Discounting life-years

Years	Males	Females	Discount	Males discounted	Females discounted
85	0.2762	0.4367	0.0537	0.0148	0.0235
86	0.2406	0.3964	0.0519	0.0125	0.0206
87	0.2068	0.3561	0.0501	0.0104	0.0179
88	0.1757	0.3158	0.0484	0.0085	0.0153
89	0.1464	0.2761	0.0468	0.0069	0.0129
90	0.1198	0.2374	0.0452	0.0054	0.0107
91	0.0971	0.2009	0.0437	0.0042	0.0088
92	0.0774	0.1667	0.0422	0.0033	0.0070
93	0.0601	0.1355	0.0408	0.0025	0.0055
94	0.0457	0.1075	0.0394	0.0018	0.0042
95	0.0338	0.0839	0.0381	0.0013	0.0032
96	0.0244	0.0638	0.0368	0.0009	0.0023
97	0.0172	0.0473	0.0355	0.0006	0.0017
98	0.0116	0.0343	0.0343	0.0004	0.0012
99	0.0076	0.0240	0.0332	0.0003	0.0008
100	0.0049	0.0164	0.0321	0.0002	0.0005
Average life expectancy	76.4000	81.0400		26.9800	27.4000

TABLE 52 Sensitivity and specificity for rapid tests – combined vaginal or rectal result against combined vaginal or rectal enriched culture reference

Parameter	Value (95% CI)	Source
PCR test		
Sensitivity	0.84 (0.79–0.88)	GBS study
Specificity	0.87 (0.85–0.89)	GBS study
PCR test given positive risk factors		
Sensitivity	0.84 (0.75–0.91)	GBS study
Specificity	0.82 (0.76–0.87)	GBS study
PCR test given negative risk factors		
Sensitivity	0.84 (0.78–0.89)	GBS study
Specificity	0.89 (0.86–0.91)	GBS study
OIA test		
Sensitivity	0.72 (0.66–0.78)	GBS study
Specificity	0.56 (0.53–0.59)	GBS study
OIA test given positive risk factors		
Sensitivity	0.75 (0.63–0.85)	GBS study
Specificity	0.59 (0.50–0.67)	GBS study
OIA test given negative risk factors		
Sensitivity	0.70 (0.62–0.77)	GBS study
Specificity	0.56 (0.53–0.60)	GBS study
OIA, optical immunoassay; PCR, polymerase chain reaction.		

Appendix 7

Decision-analytic models

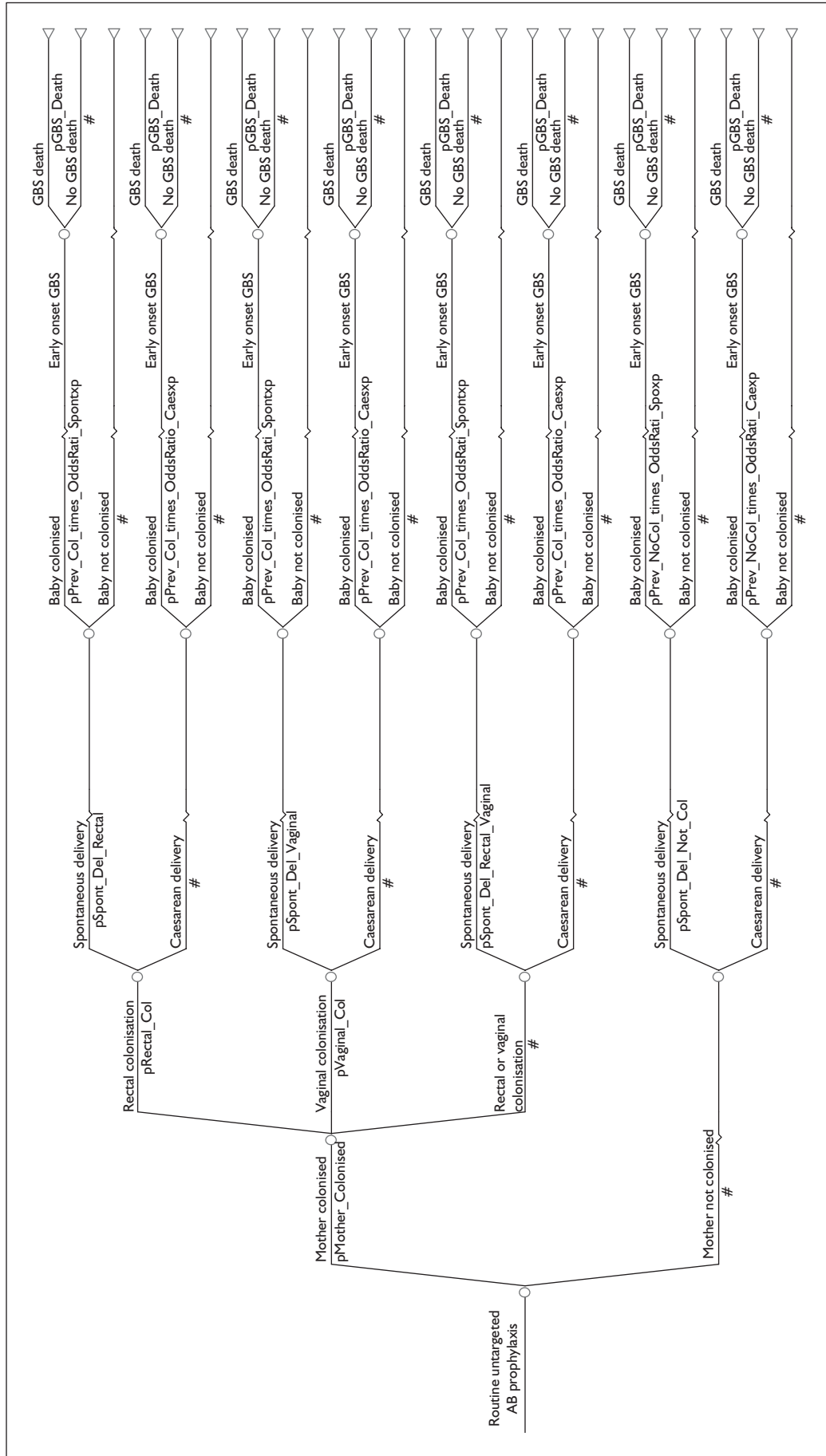


FIGURE 19 Subtree 1. AB, antibiotic.

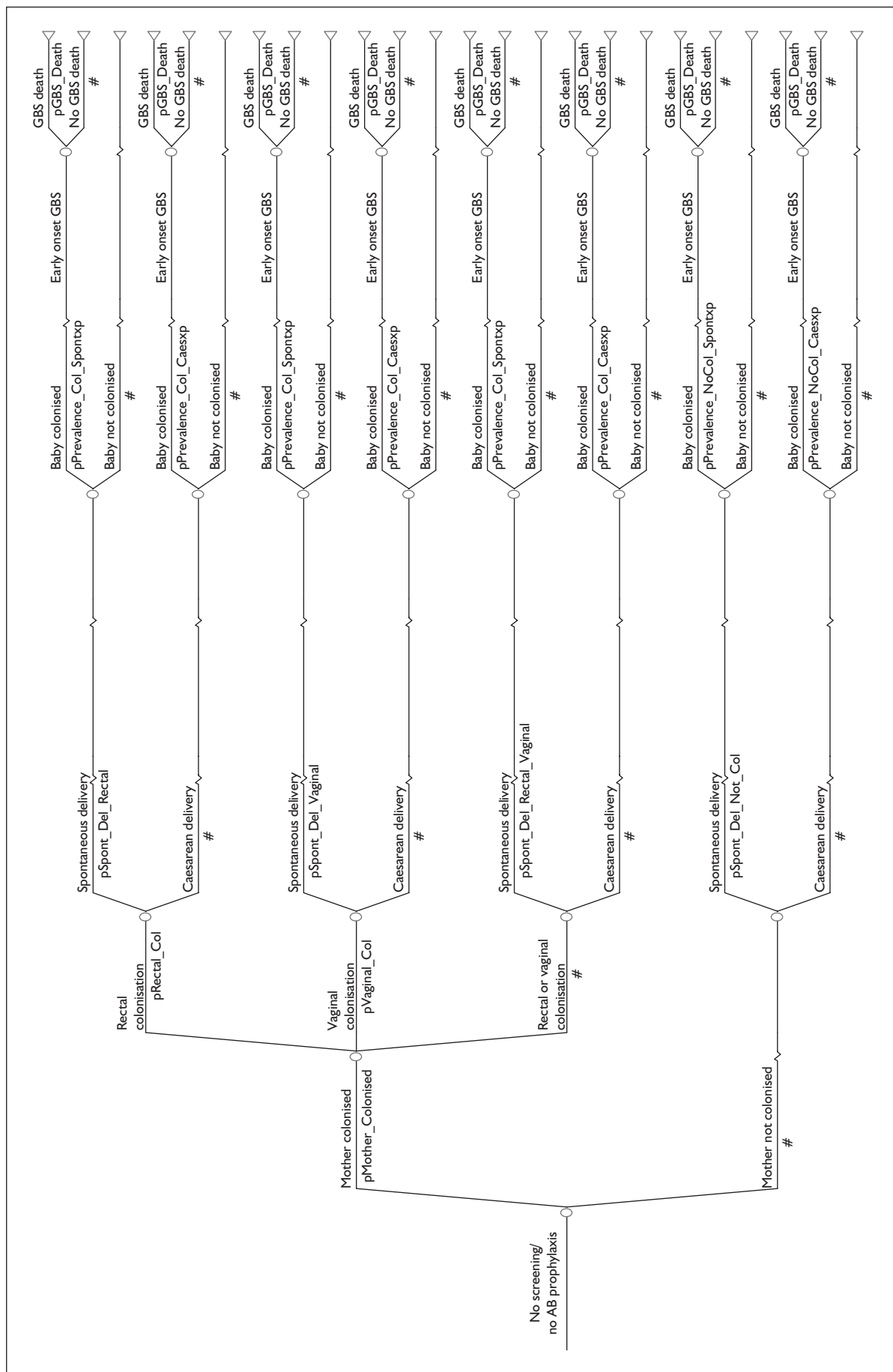


FIGURE 20 Subtree 2. AB, antibiotic.

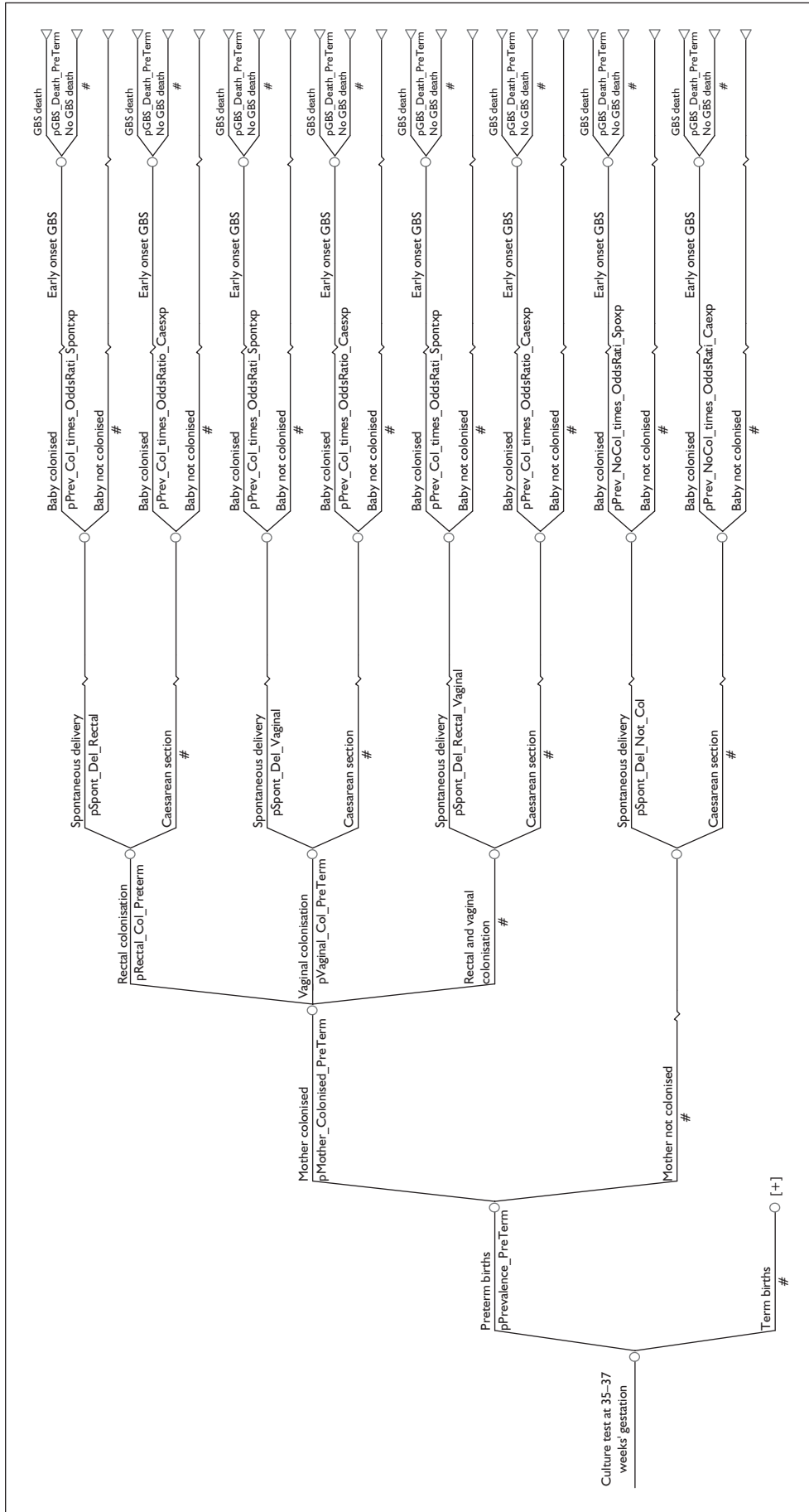


FIGURE 21 (a) Subtree 3.

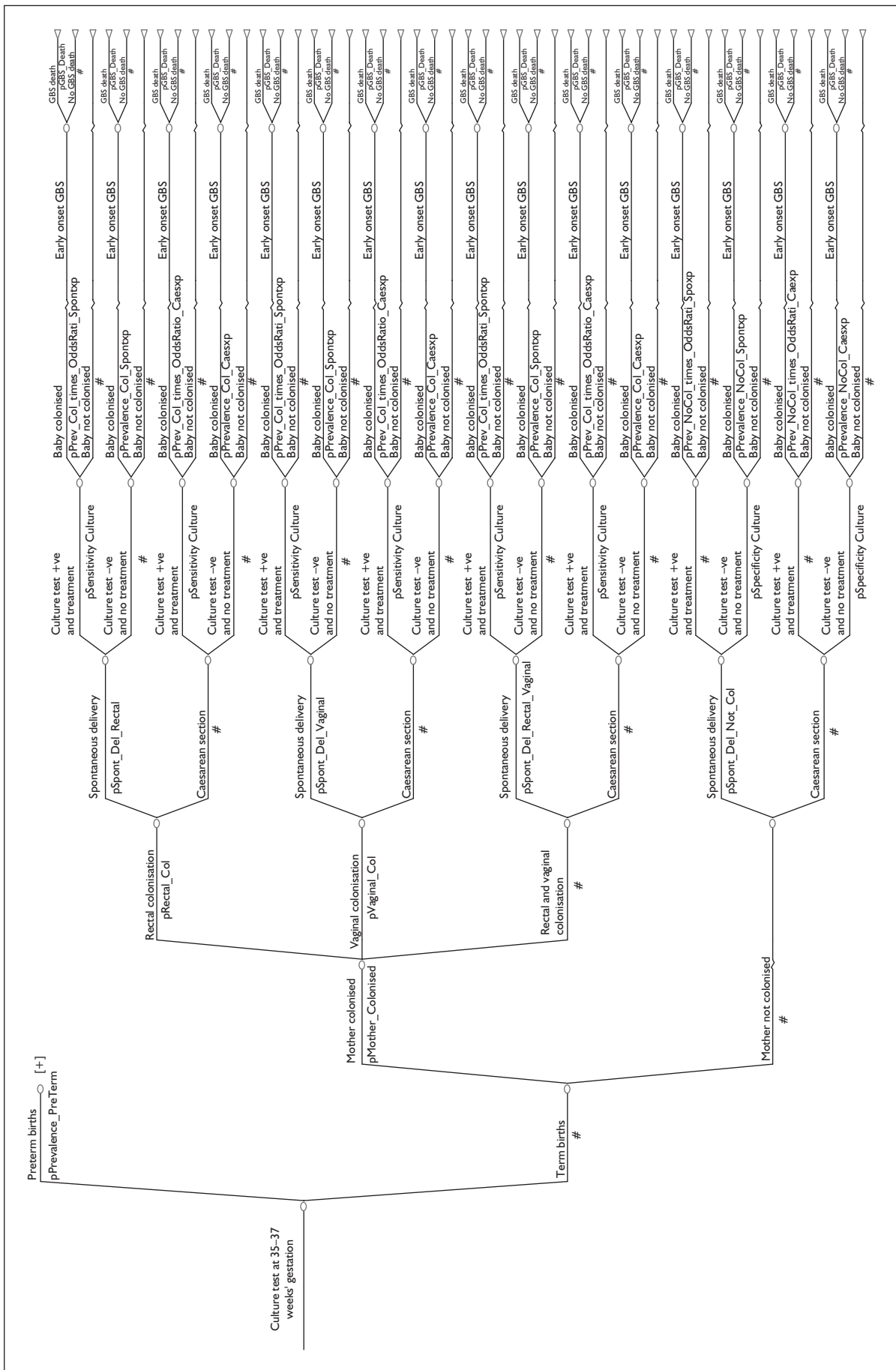


FIGURE 21 (b) Subtree 3 (continued).

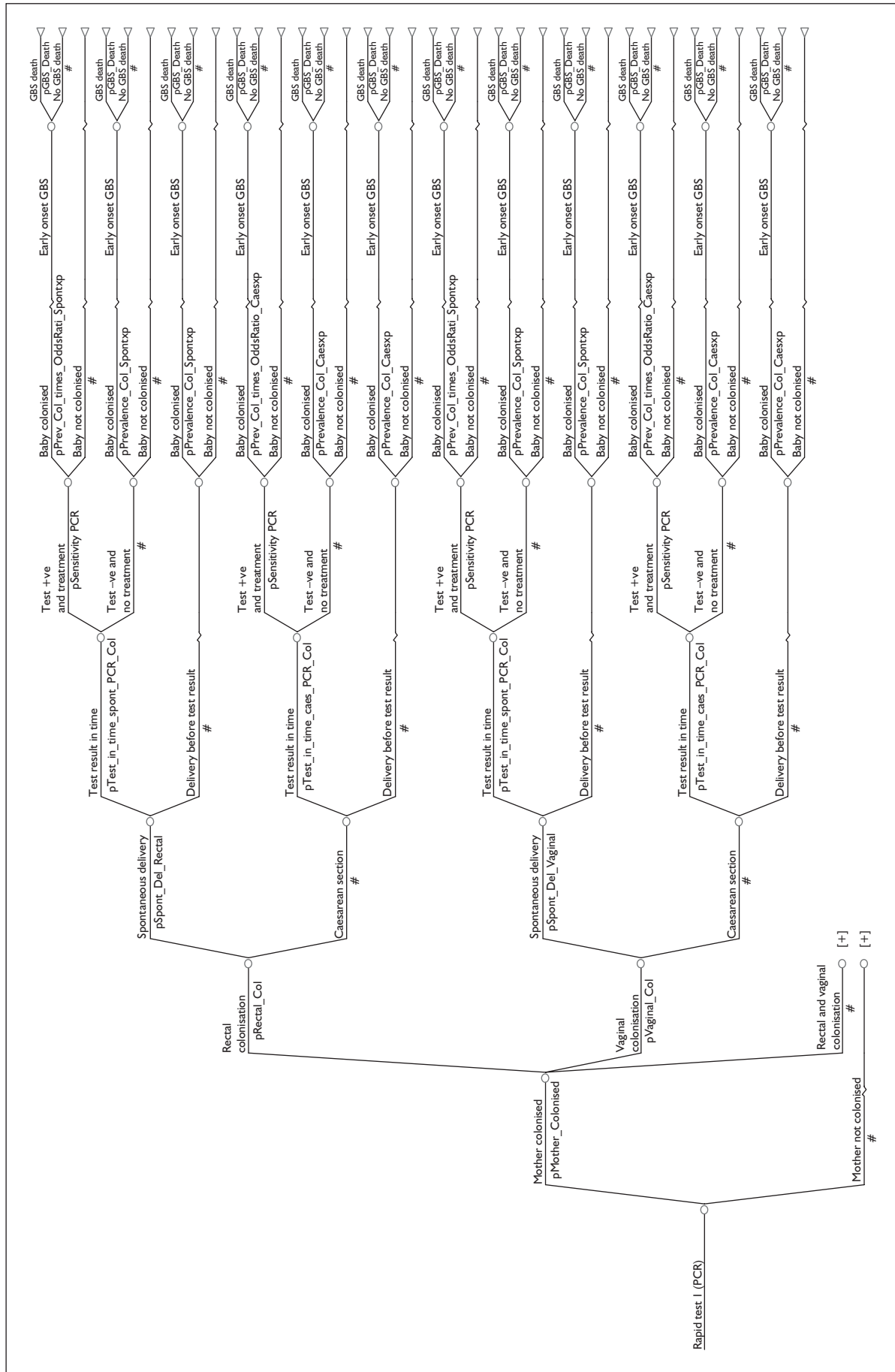


FIGURE 22 (a) Subtree 4.

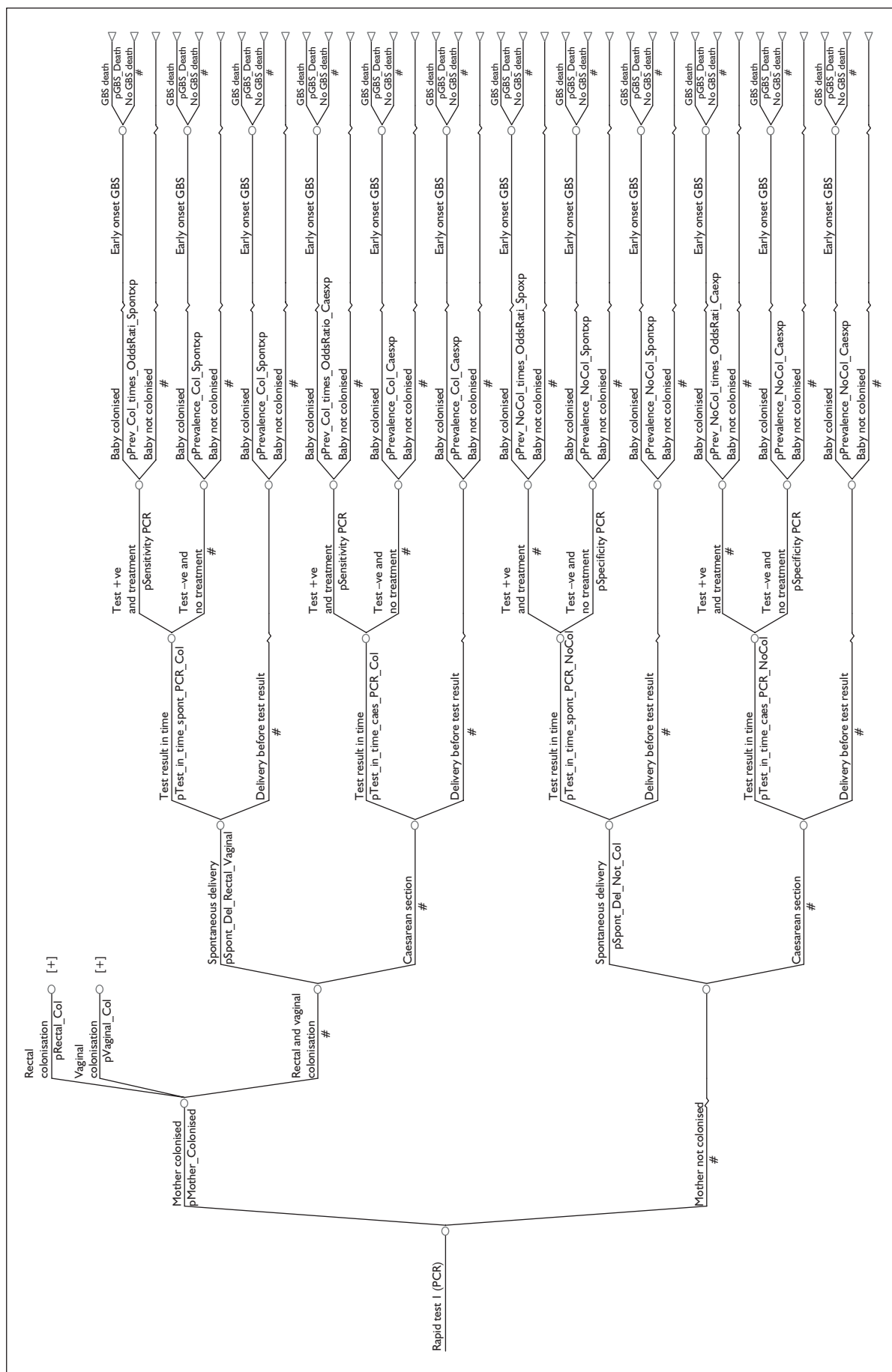


FIGURE 22 (b) Subtree 4 (continued).

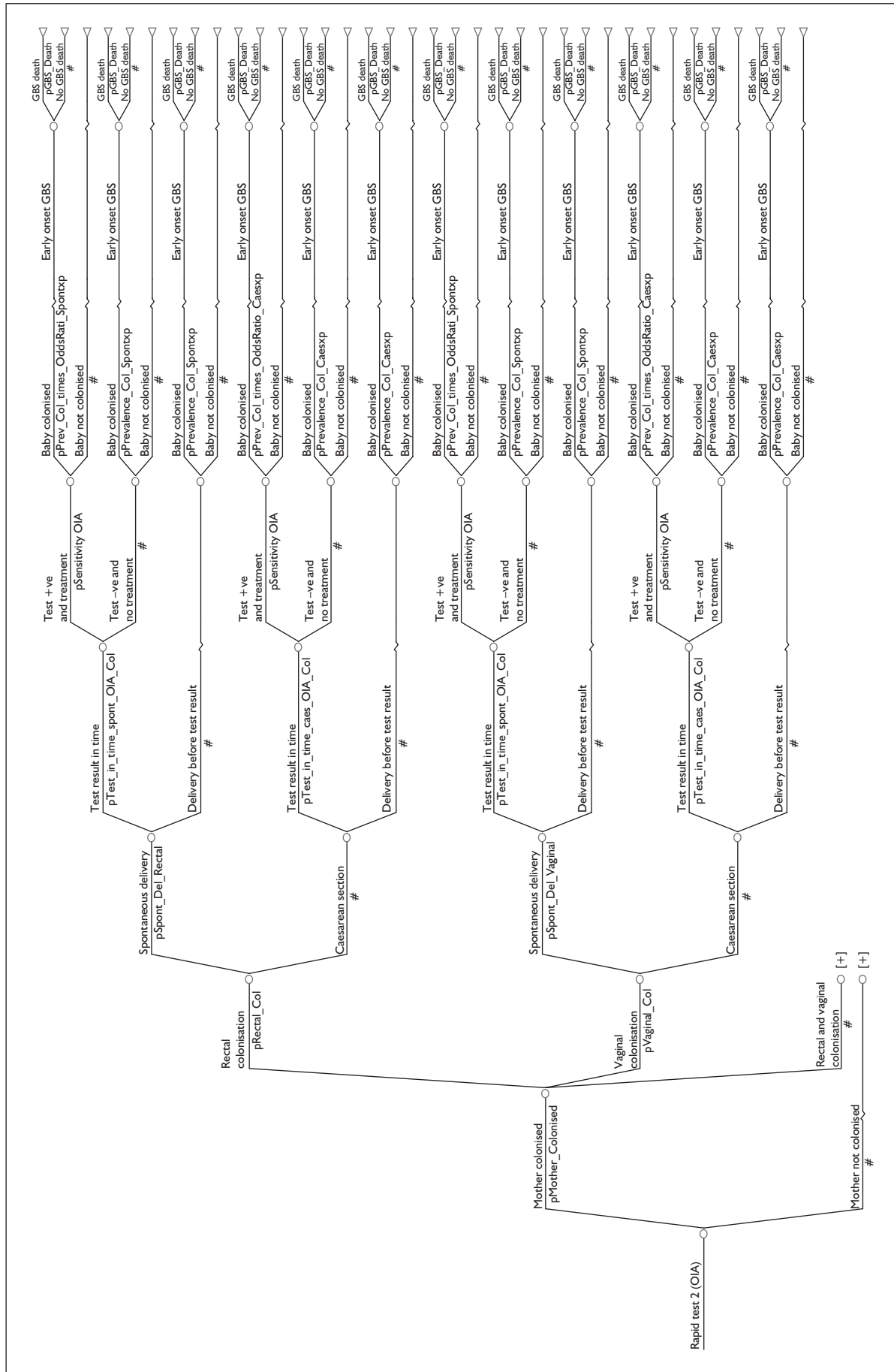


FIGURE 23 (a) Subtree 5.

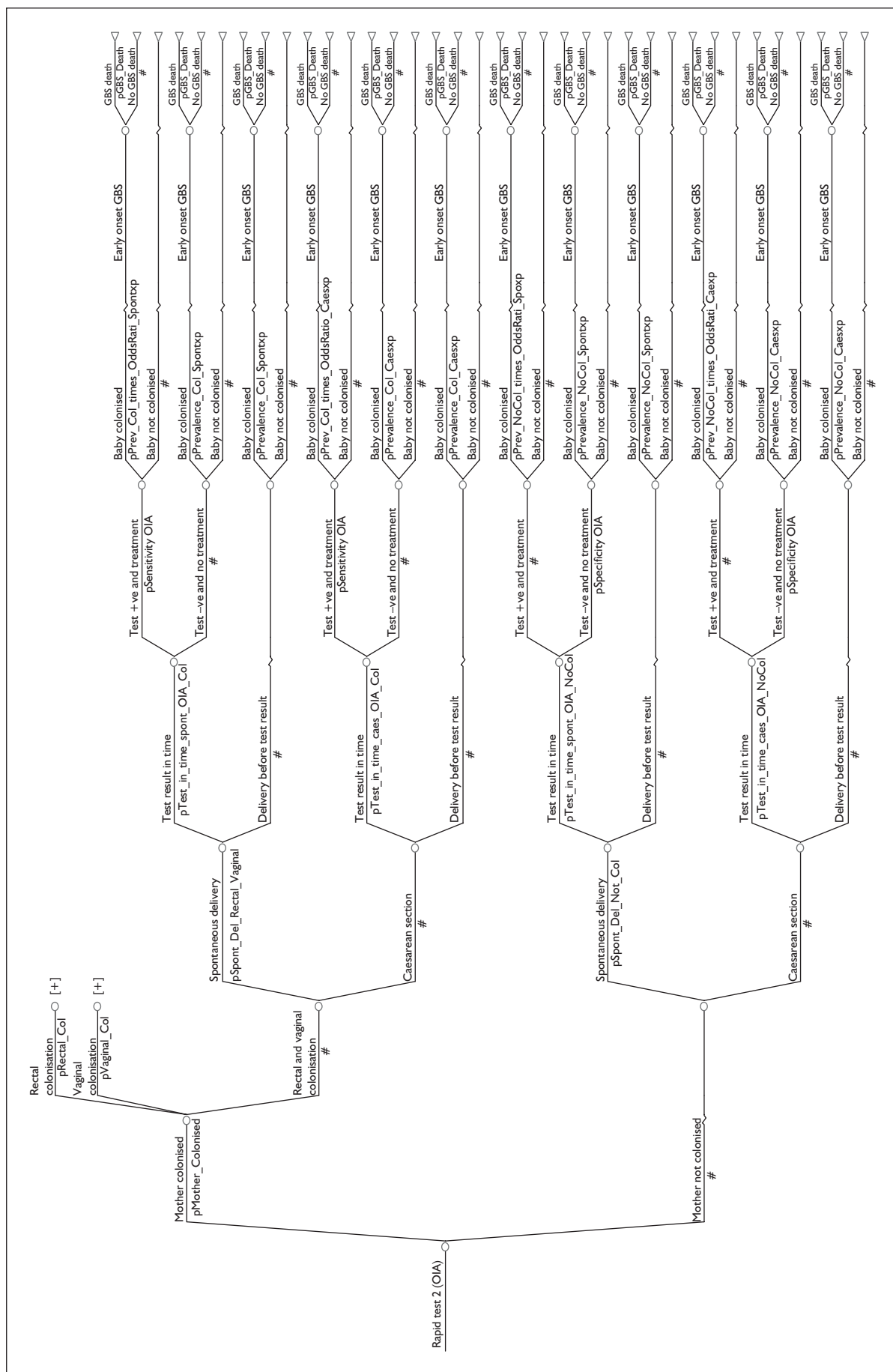


FIGURE 23 (b) Subtree 5 (continued).

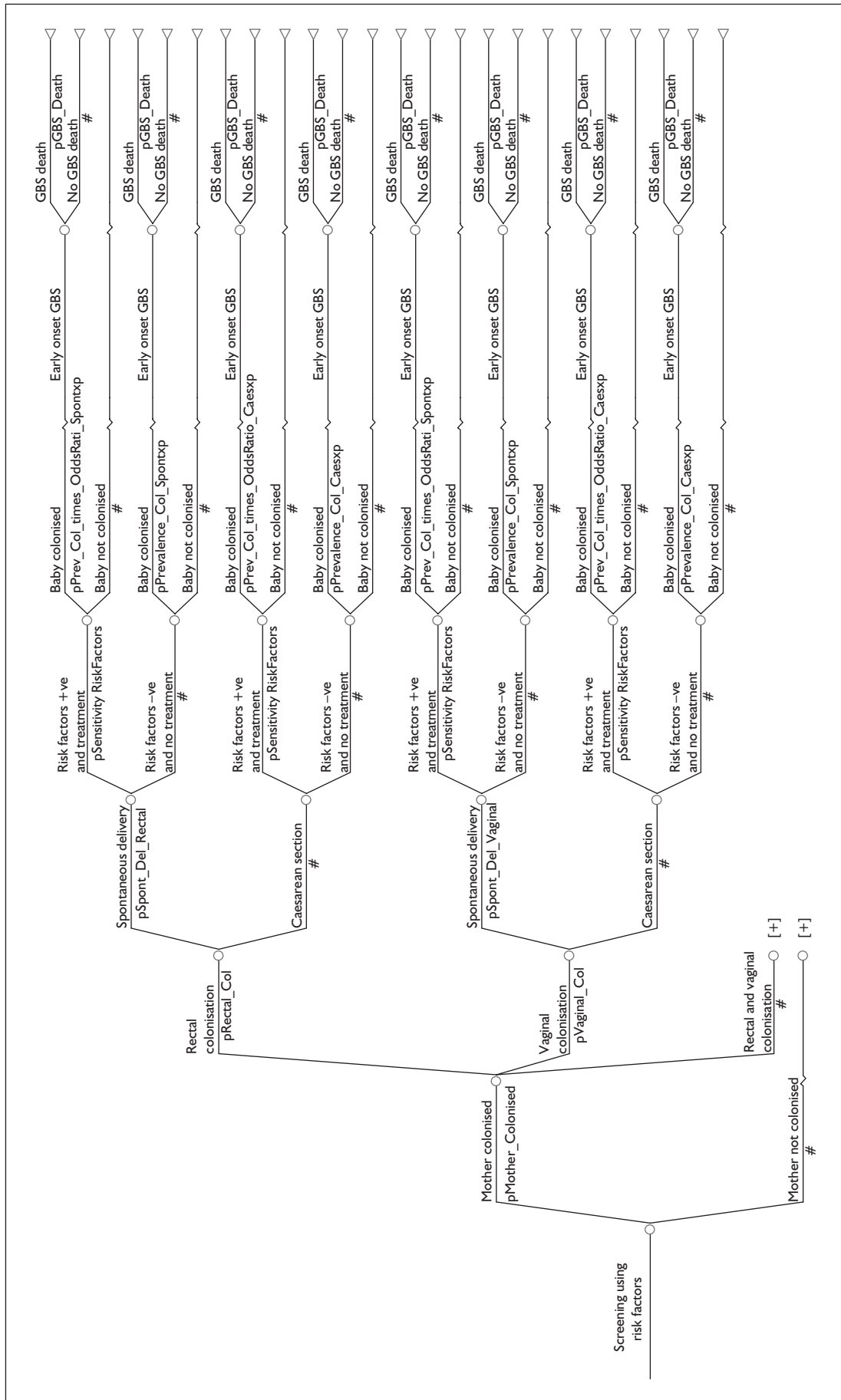


FIGURE 24 (a) Subtree 6.

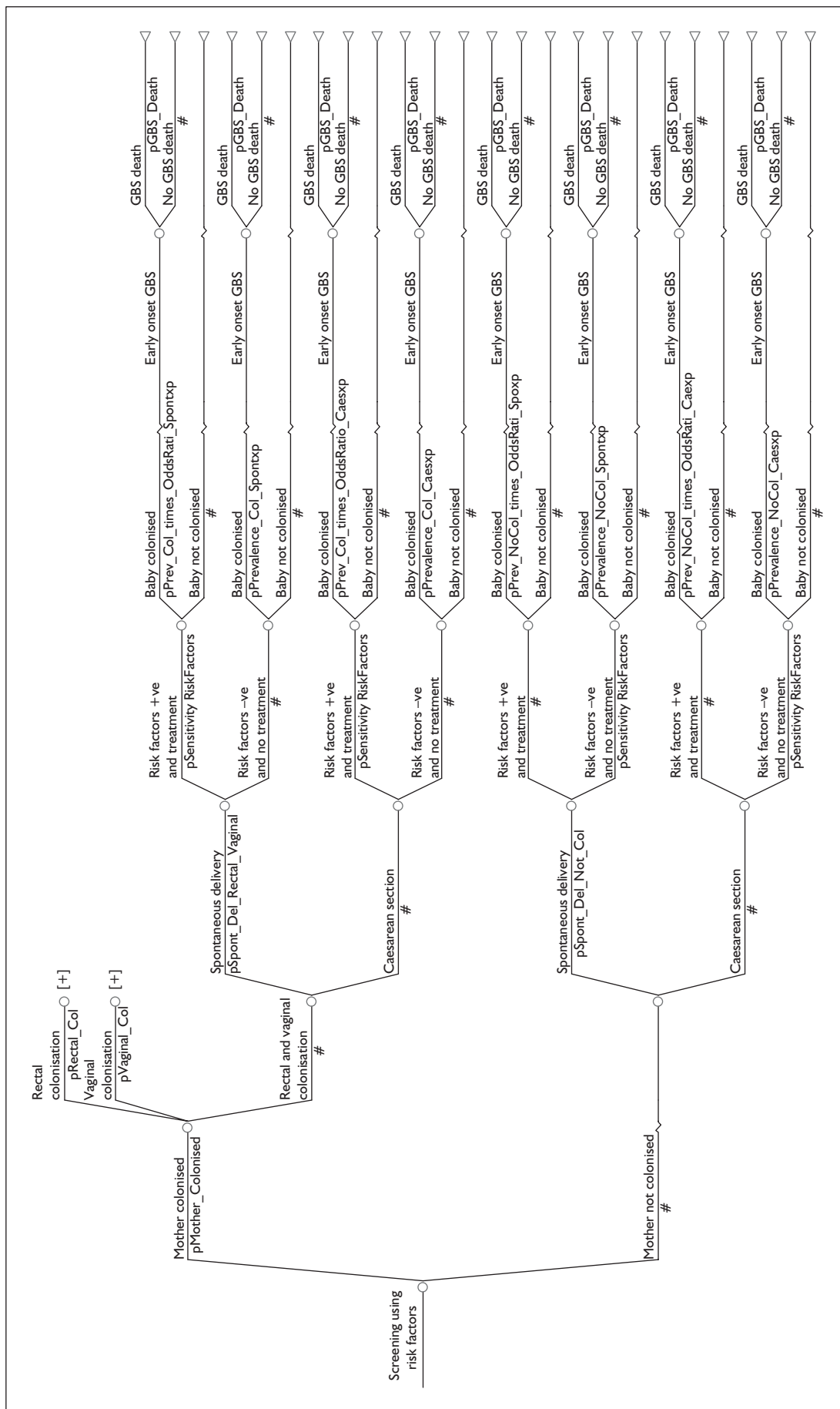


FIGURE 24 (b) Subtree 6 (continued).

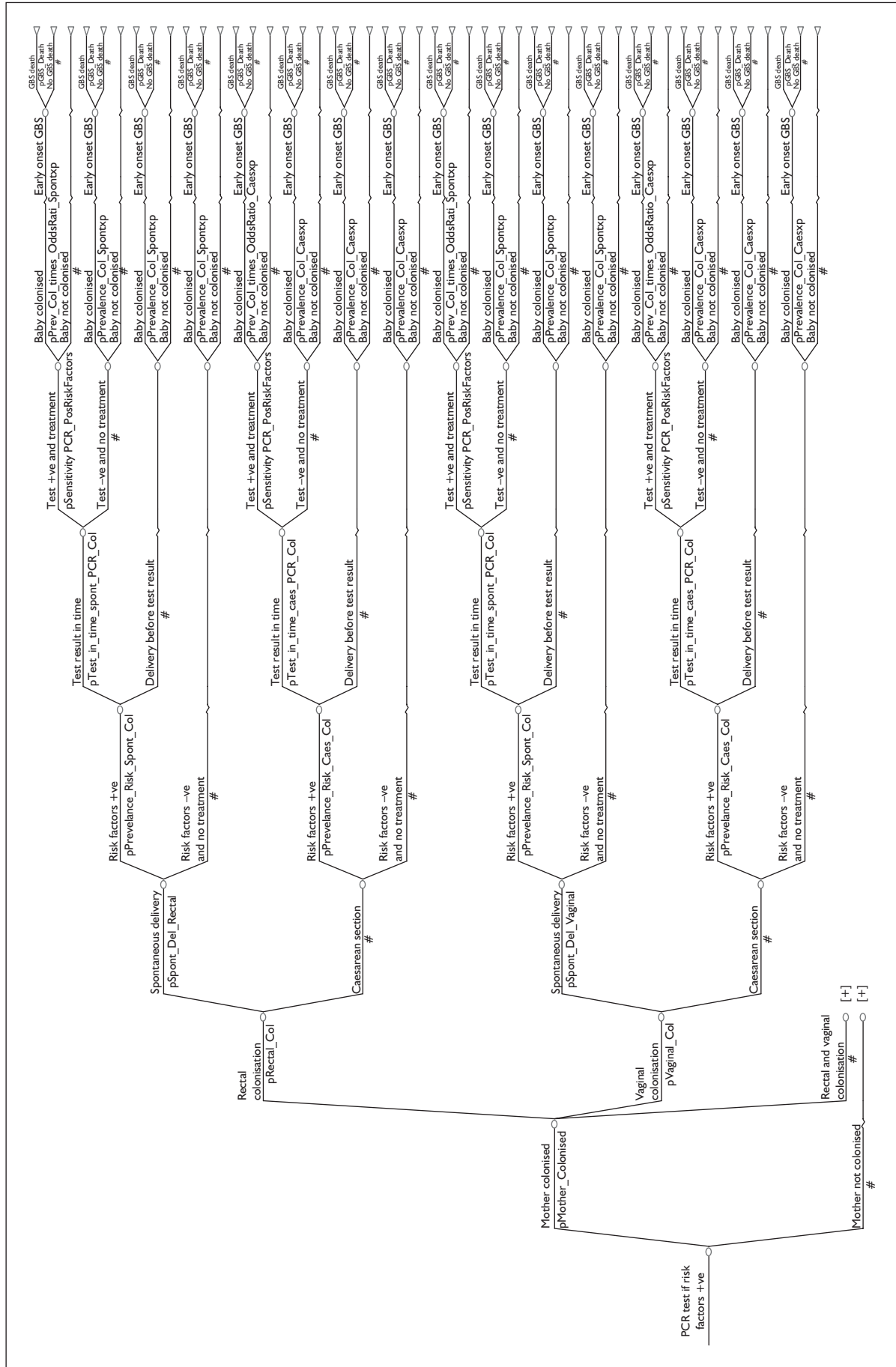


FIGURE 25 (a) Subtree 7.

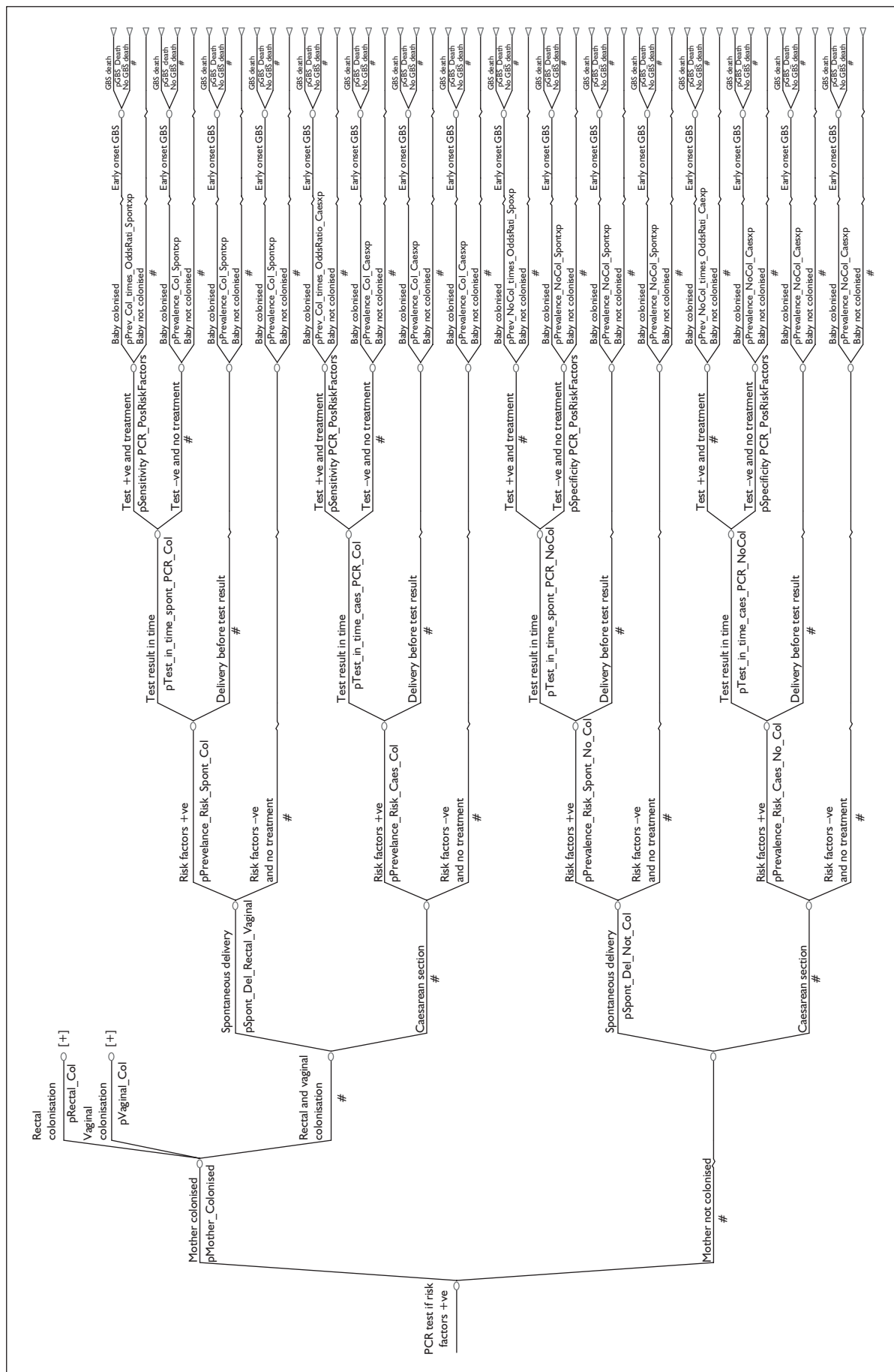


FIGURE 25 (b) Subtree 7 (continued).

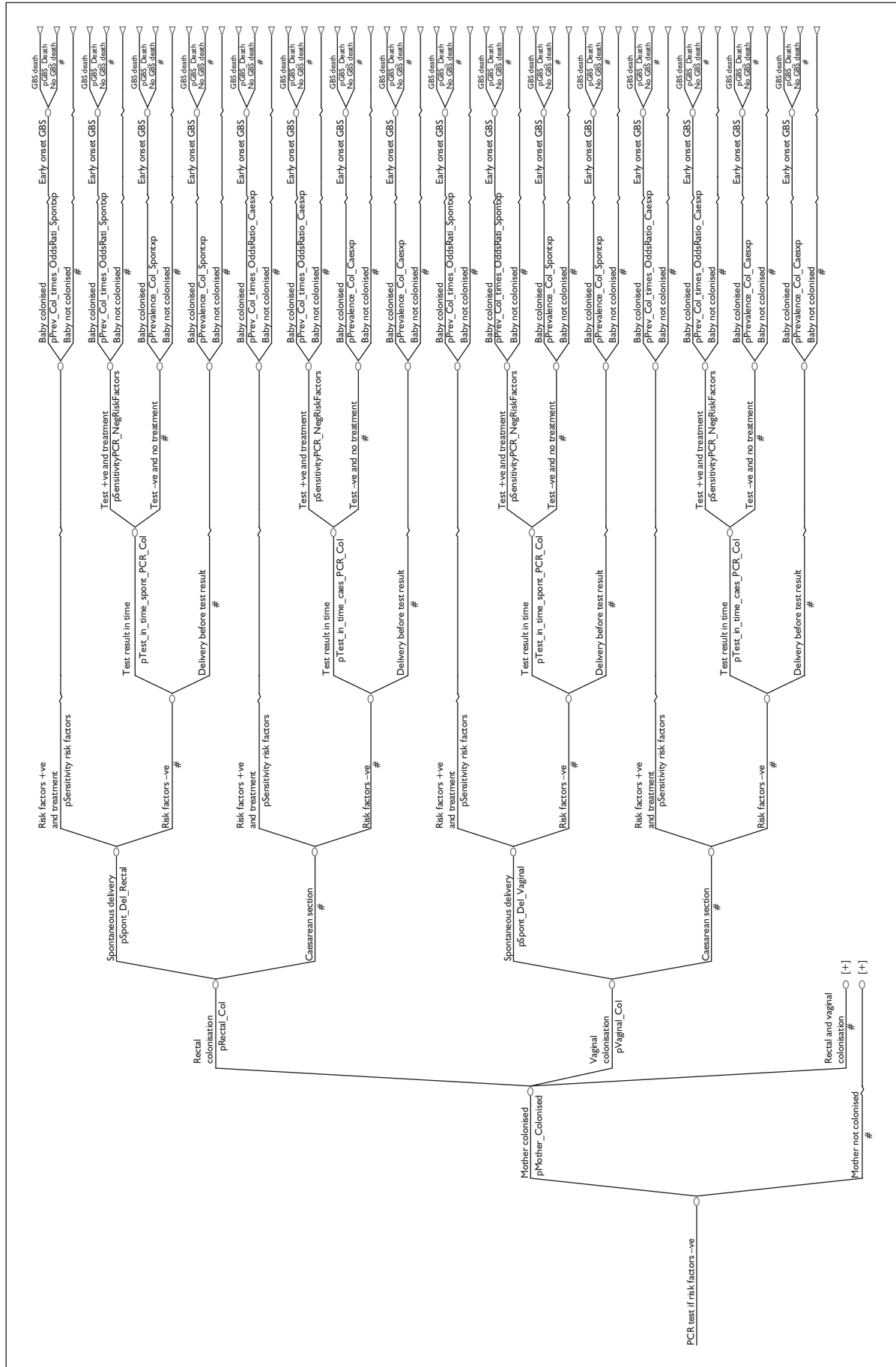


FIGURE 26 (a) Subtree 8.

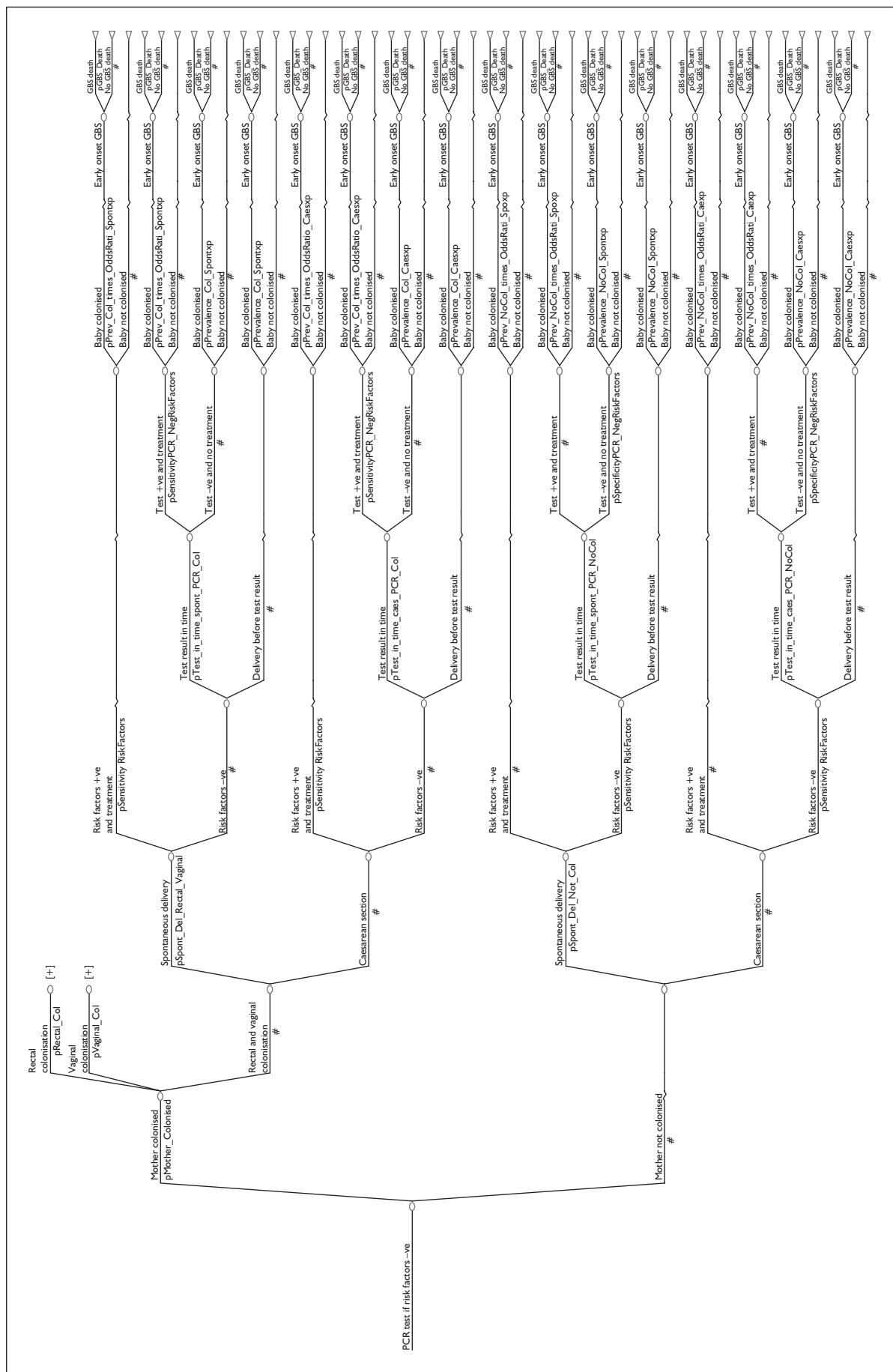


FIGURE 26 (b) Subtree 8 (continued).

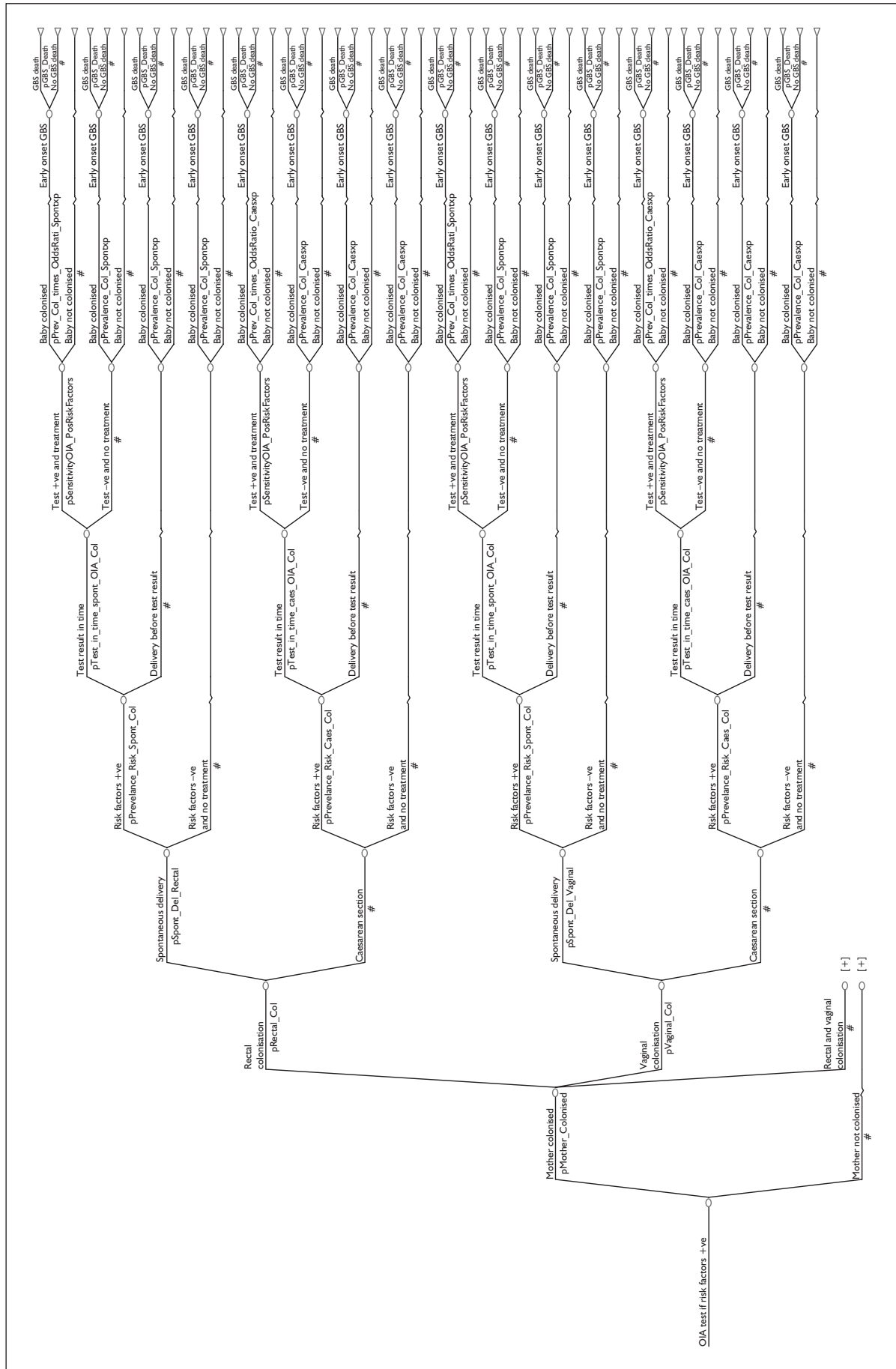


FIGURE 27 (a) Subtree 9.

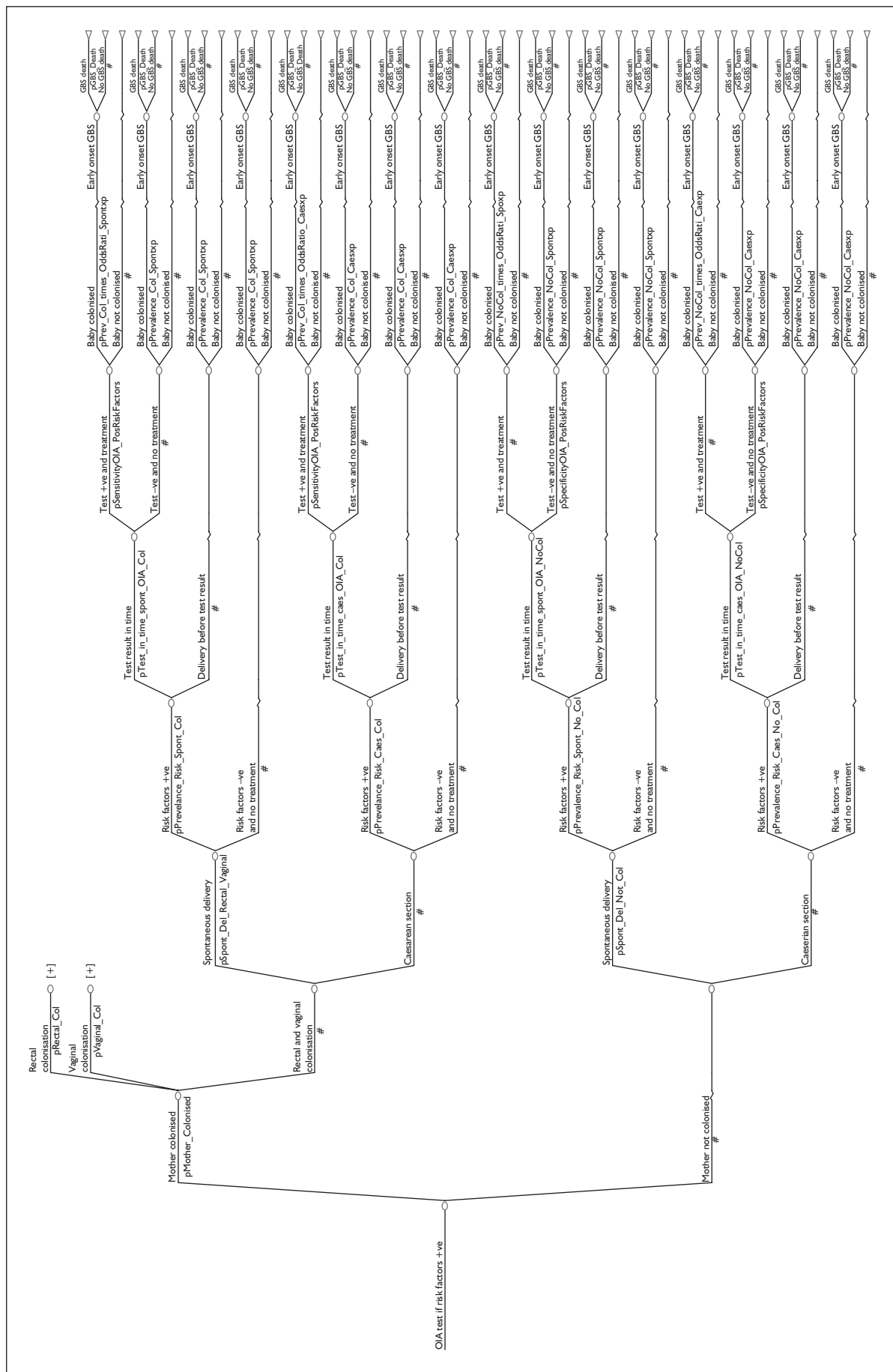


FIGURE 27 (b) Subtree 9 (continued).

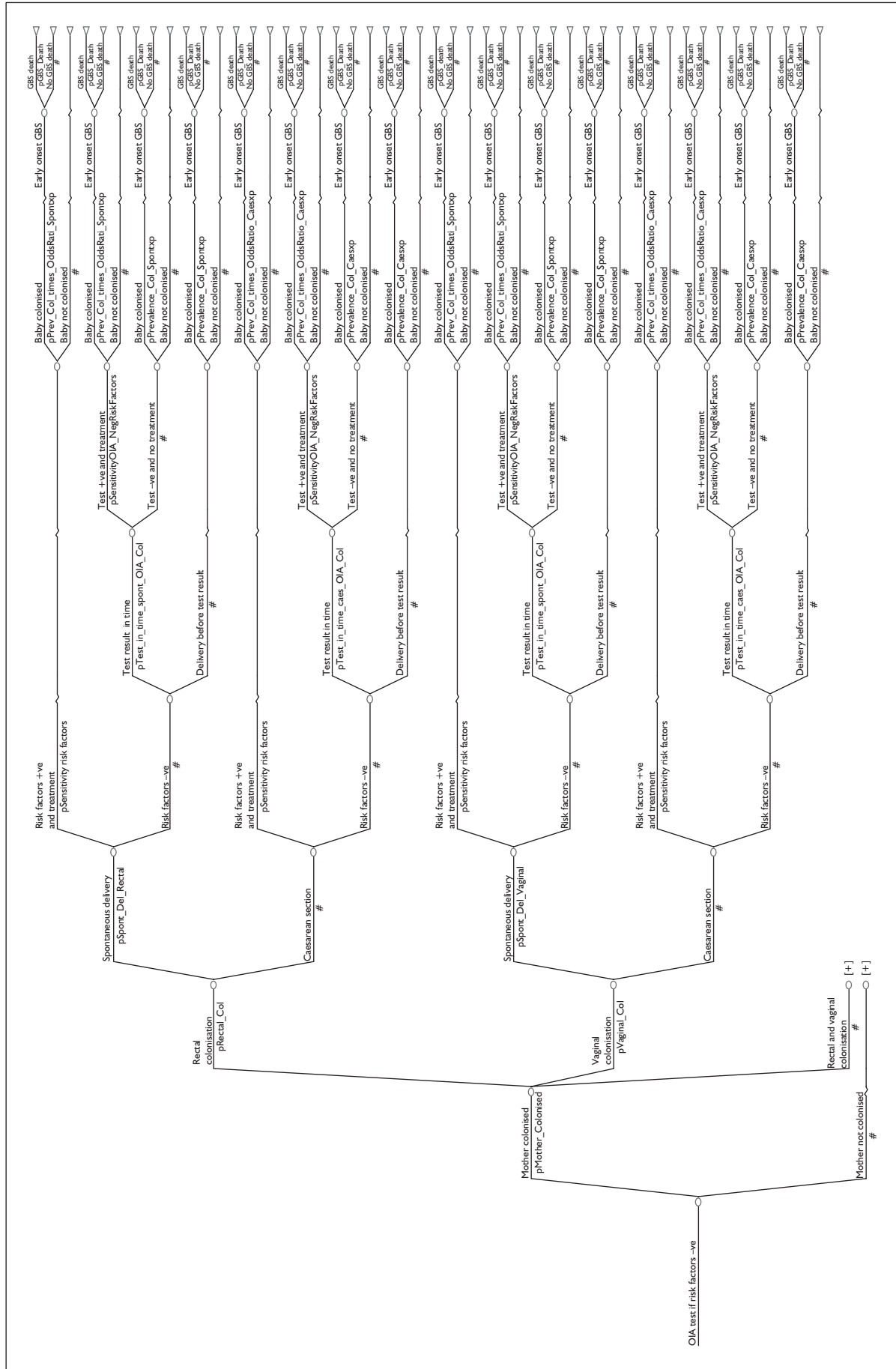


FIGURE 28 (a) Subtree 10.

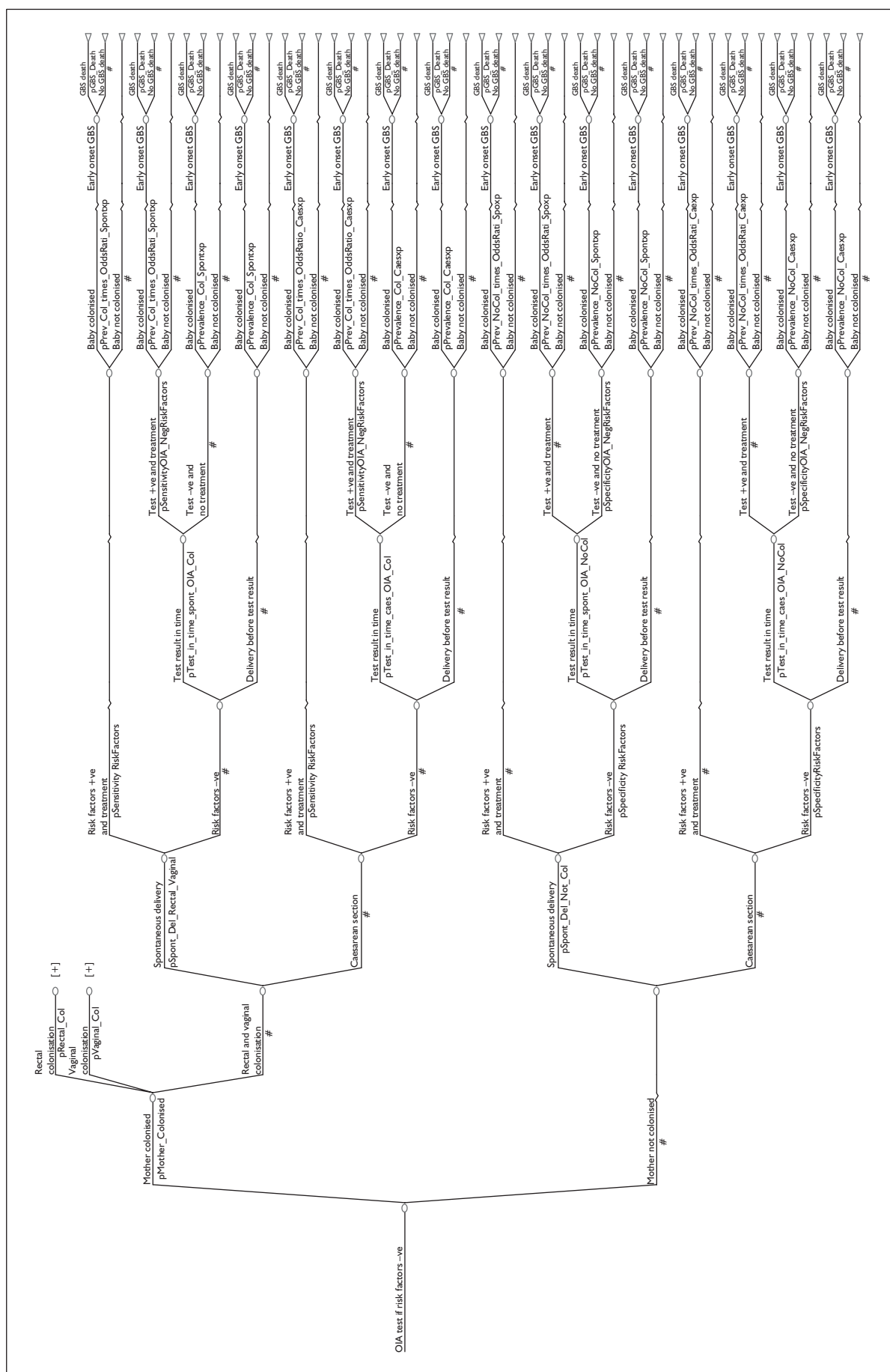


FIGURE 28 (b) Subtree 10 (continued).

Appendix 8

Deterministic sensitivity analysis

Outcome of cost per case of EOGBS disease avoided

In *Tables 53* and *54* the summarised results of the sensitivity analysis are presented for analyses 1 and 2 respectively. For both analyses the results are based on an outcome of EOGBS disease cases avoided.

Changing the cost associated with EOGBS disease

In all cases and for both analyses there is no significant effect on the ICER of different estimates for the cost of EOGBS disease. Changes in these costs would not change any decision made on the basis of the base-case ICER.

Changing the cost associated with the culture test at 35–37 weeks

For analysis 1, if the cost associated with the culture test at 35–37 weeks could be reduced from its base-case estimated cost of £10.63 to £7, the strategy of culture at 35–37 weeks would become the preferred strategy as the ICER for this strategy compared with doing nothing would be £39,578 per case of EOGBS disease avoided.

For analysis 2, when the strategy of routine untargeted antibiotics to all is removed from the analysis, culture, which costs £10.63, becomes the preferred and most cost-effective strategy in the base case. However, for a relatively very small increase in the cost of culture (i.e. an increase of less than £1.50 to £12), screening based on culture is no longer the most cost-effective strategy and risk factors would be the most cost-effective strategy.

Changing the estimated effect of intravenous antibiotic therapy on EOGBS and death given maternal colonisation

The OR used by Colbourn *et al.*⁶⁹ was much lower at 0.028 (95% CI 0.0015–0.12) than that used in this study. When this OR is used in the current model there is a significant effect on the ICER.

For analysis 1, which includes all options, the most cost-effective strategy of providing antibiotic prophylaxis to all remains the most cost-effective strategy but the new estimated ICER is £30,840

per case of EOGBS disease avoided, which is lower than that estimated in the base case.

For analysis 2, which excludes antibiotics as a strategy, the ICER for the relatively most cost-effective strategy of screening based on culture at 35–37 weeks falls from £52,810 per case of EOGBS disease avoided in the base case to £40,669 based on the alternative estimated treatment effect.

Changing the PCR rapid test sensitivity and specificity from that based on the vaginal swab only (base case) to that of the rectal and vaginal swabs combined

This change in PCR rapid test sensitivity and specificity from that based on the vaginal swab only (base case) to that of the rectal and vaginal swabs combined had no effect on the results.

Threshold analysis for the cost of the rapid test (based on vaginal swabs only)

The cost of the rapid test was estimated to be £29.95 in the current study.

For analysis 1 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 rapid test could be reduced to as low as £4.50, it would become the most cost-effective strategy and is likely to be accepted by decision-makers.

For analysis 2 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 rapid test could be reduced to as low as £6.50 it would become the most cost-effective strategy.

Threshold analysis for the cost of the rapid test (based on vaginal and rectal swabs combined)

For analysis 1 the threshold analysis shows that, given current accuracy in terms of sensitivity and specificity, and based on the vaginal and rectal swabs combined, if the cost of the rapid test could fall to as low as £6.00 it would become the most cost-effective strategy and is likely to be accepted by decision-makers.

For analysis 2, in which the strategy of routine untargeted antibiotics to all is removed from the analysis, the threshold analysis shows that, given current accuracy in terms of sensitivity and specificity, and based on the vaginal and rectal swabs combined, if the cost of the rapid test could fall to as low as £9.50, it would become the most cost-effective strategy.

Threshold analysis for the cost of antibiotics (based on vaginal swabs only)

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 strategy when the cost of antibiotics is raised to £21.50, at which stage the strategy of culture at 35–37 weeks also becomes a potential contender with an ICER of £60,225. 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 is the preferred strategy regardless of the cost of antibiotics. For example, this strategy remains the preferred option even when the cost of antibiotics is raised to £50

Removing the assumption that all women who deliver before the screening test based on culture at 35–37 weeks are treated with antibiotic prophylaxis (analysis 2 only)

When the assumption that all women who deliver before 35 weeks are treated with antibiotic prophylaxis is removed there is no impact on the decision to be made, but the value of the ICER for the strategy of culture at 35–37 weeks goes up by nearly £1500 from the base-case value of £52,810 to £54,288 per case of EOGBS disease avoided.

TABLE 53 Analysis 1 – summary of the main results and sensitivity analysis in terms of cost, effectiveness and incremental cost-effectiveness ratios (ICERs) based on an outcome of cost per case of early-onset group B streptococcus (EOGBS) disease avoided

Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER (£)
Base-case results ^a	1069	14.06	0.999877	0.000353	39,813
A. Changing the cost associated with EOGBS disease					
Halving the cost: EOGBS death = £769; EOGBS no death = £267	1069	14.17	0.999877	0.000353	40,117
Doubling the cost: EOGBS death = £3076; EOGBS no death = £1068	1069	13.85	0.999877	0.000353	39,204
B. Changing the cost associated with the culture test					
Culture test costs £7	1065	10.07	0.999778	0.000254	39,578
Culture test costs £7.50	1069	14.06	0.999877	0.000353	39,813
C. Changing the estimated effect of intravenous antibiotic therapy on EOGBS given maternal colonisation					
Alternative estimated treatment effect for antibiotics = 0.028 (OR) ⁶⁴	1069	14.00	0.999978	0.000454	30,840
D. Changing the rapid test PCR sensitivity and specificity from that based on vaginal swab only to that based on vaginal and rectal swabs combined					
Combined swabs: sensitivity = 0.84; specificity = 0.87	1069	14.06	0.999877	0.000353	39,813
E. 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 (based on vaginal swab)					
PCR test costs £4.50	1062	6.88	0.9997	0.000176	39,090
PCR test costs £5	1069	14.06	0.999877	0.000353	39,813

continued

TABLE 53 Analysis 1 – summary of the main results and sensitivity analysis in terms of cost, effectiveness and incremental cost-effectiveness ratios (ICERs) based on an outcome of cost per case of early-onset group *B. streptococcus* (EOGBS) disease avoided (continued)

	Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER (£)
F. 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 (based on combined vaginal and rectal swabs)						
PCR test costs £6	Rapid test 1 (PCR)	1064	9.61	0.999777	0.000254	37,855
PCR test costs £6.50	Routine untargeted IAP to all	1069	14.06	0.999877	0.000353	39,813
G. Changing the cost associated with antibiotics prophylaxis and treatment						
IAP cost £21.00	Routine untargeted IAP	1076	20.78	0.999877	0.000353	58,835 ^b
IAP cost £21.50	Culture test at 35–37 weeks	1070	15.32	0.999778	0.000254	60,225 ^b
	Routine untargeted IAP	1076	5.97	0.999877	0.000099	60,314 ^c

IAP; intravenous antibiotic prophylaxis; OR, odds ratio; PCR, polymerase chain reaction.
 a For base case, cost for EOGBS death is £1538; estimated effect of intravenous antibiotic therapy on EOGBS given maternal colonisation is 0.17 (OR based on Cochrane estimate³⁶); sensitivity and specificity used for rapid test PCR based on vaginal swab only are 0.584 and 0.923 respectively.

TABLE 54 Analysis 2 – summary of the main results and sensitivity analysis in terms of cost, effectiveness and incremental cost-effectiveness ratios (ICERs) based on an outcome of cost per case of early-onset group *B streptococcus* (EOGBS) disease avoided

Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER (£)
Base case ^a	1068	13.43	0.999778	0.000254	52,810
A. Changing the cost associated with EOGBS disease					
Halving the cost: EOGBS death = £769; EOGBS no death = £267	1068	13.51	0.999778	0.000254	53,113
Doubling the cost: EOGBS death = £3076; EOGBS no death = £1068	1068	13.28	0.999778	0.000254	52,205
B. Changing the cost associated with the culture test					
Cost of culture test is £11.50	1069	14.24	0.999778	0.000254	55,981
Cost of culture test is £12	1061	6.12	0.999631	0.000107	57,038
Culture test at 35–37 weeks	1069	8.58	0.999778	0.000147	58,362 ^b
C. Changing the estimated effect of intravenous antibiotic therapy on EOGBS given maternal colonisation					
Alternative estimated treatment effect for antibiotics = 0.028 (OR) ⁶⁴	1068	13.38	0.999853	0.000329	40,669
D. Changing the rapid test PCR sensitivity and specificity from that based on vaginal swab only to that based on vaginal and rectal swabs combined					
Combined swabs: sensitivity = 0.84; specificity = 0.87	1068	13.43	0.999778	0.000254	52,810
continued					

TABLE 54 Analysis 2 – summary of the main results and sensitivity analysis in terms of cost, effectiveness and incremental cost-effectiveness ratios (ICERs) based on an outcome of cost per case of early-onset group *B. streptococcus* (EOGBS) disease avoided

Test/treatment combination	Mean cost per woman (£)	Difference in costs (£)	Effectiveness	Absolute risk reduction	ICER (£)
E. 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 (based on vaginal swab)					
PCR test costs £6.50					
Rapid test 1 (PCR)	1064	8.88	0.9997	0.000176	50,451
Culture test at 35–37 weeks	1068	4.55	0.999778	0.000078	58,113 ^b
Culture test at 35–37 weeks	1068	13.43	0.999778	0.000254	52,810
F. 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 (based on combined vaginal and rectal swabs)					
PCR test costs £9.50					
Rapid test 1 (PCR)	1068	13.11	0.999777	0.000254	51,642
PCR test if risk factors negative	1071	2.83	0.999805	0.000028	101,933 ^b
Culture test at 35–37 weeks	1068	13.43	0.999778	0.000254	52,810
PCR test if risk factors negative	1071	2.89	0.999805	0.000027	106,067 ^b
G. Changing the cost associated with treatment					
IAP cost £50.00					
Culture test at 35–37 weeks	1077	22.76	0.999778	0.000254	89,498
H. Not giving untargeted antibiotics to all preterm babies					
Culture test at 35–37 weeks	1067	12.41	0.999752	0.000229	54,288

IAP, intravenous antibiotic prophylaxis; OR, odds ratio; PCR, polymerase chain reaction.

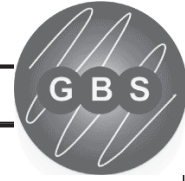
a For base case, cost for EOGBS death is £1538; estimated effect of intravenous antibiotic therapy on EOGBS given maternal colonisation is 0.17 (OR based on Cochrane estimate³⁶); sensitivity and specificity used for rapid test PCR based on vaginal swab only are 0.584 and 0.923 respectively.

b ICER presented incrementally compared with value presented directly above it.

Appendix 9

Data collection forms

Version 1.1 Date: 24/01/05

GBS Study Data Collection Form 1**FORM 1** to be completed by Hospital Midwife and collected in GBS Study Collection Box

Hospital Number: Study Number:
 Forename(s): Surname:
 Date of birth (dd-mon-yyyy):

If using hospital stickers, please ensure that all four data collection forms are given a sticker

ADMISSION DETAILSWritten informed consent received? No Yes

Date of admission to Labour Ward (dd-mon-yyyy): Time of admission (24 hour clock):

OUTCOME

Date of delivery (dd-mon-yyyy): Time of delivery (24 hour clock):

Induction of labour? No Yes Method of delivery: Vaginal delivery Assisted vaginal delivery Caesarean section

Approx. duration of labour (hours: minutes):

INTRAPARTUM ANTIBIOTIC PROPHYLAXIS

Not offered Offered and declined Offered and given:
 Penicillin Clindamycin Amoxycillin Other (please state):

Adverse reaction to antibiotics? No Yes
 If yes, was it Anaphylaxis Other (please state):

Date of first dose: Time of first dose: Number of doses:
 (dd-mon-yyyy) (24 hour clock)

RECENT ANTIBIOTIC THERAPY

Please record whether any antibiotic therapy received during the 14 days prior to labour

None Current therapy Recent, but not current, therapy **RISK FACTORS**

Please cross all that are applicable

- Previous GBS-affected baby? GBS detected in current pregnancy?
 Intrapartum fever (>38°C)? Prolonged rupture of membranes (>18 hours)?
 Pre-term labour? Other risk factor (Please state):

SAMPLE DETAILS

Date mother's swabs collected (dd-mon-yyyy): Time mother's swabs collected (24 hour clock):

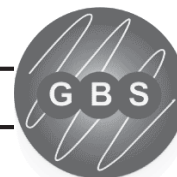
Specimen type (please indicate all tests taken):
 Lower vaginal swab No Yes
 Rectal swab No Yes
 Neonate ear swab No Yes

Date of initial diagnostic VE (at presentation of queried labour) (dd-mon-yyyy):

Time of initial diagnostic VE (at presentation of queried labour) (please use 24 hour clock):

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GBS Study Data Collection Form 2



FORM 2 to be given to Midwifery Assistant with two pairs of the Mother's swabs

Hospital Number: Study Number:
 Forename(s): Surname:
 Date of birth (dd-mon-yyyy):

If using hospital stickers, please ensure that all four data collection forms are given a sticker

MIDWIFERY ASSISTANT TO COMPLETE THE FOLLOWING

Name of the person performing the tests:

OIA VAGINAL SWAB

Time test commenced (24 hour clock):

Time result available (24 hour clock):

Date of test (dd-mon-yyyy):

- Result:
- Negative for GBS
 - Positive for GBS
 - Not done
 - Unclear
 - Failed
 - No swab

Notes inc. reason for failure:

.....

OIA RECTAL SWAB

Time test commenced (24 hour clock):

Time result available (24 hour clock):

Date of test (dd-mon-yyyy):

- Result:
- Negative for GBS
 - Positive for GBS
 - Not done
 - Unclear
 - Failed
 - No swab

Notes inc. reason for failure:

.....

PCR VAGINAL SWAB

Time test commenced (24 hour clock):

Time result available (24 hour clock):

Date of test (dd-mon-yyyy):

- Result:
- Negative for GBS
 - Positive for GBS
 - Not done
 - Unclear
 - Failed
 - No swab

Notes inc. reason for failure:

.....

PCR RECTAL SWAB

Time test commenced (24 hour clock):

Time result available (24 hour clock):

Date of test (dd-mon-yyyy):

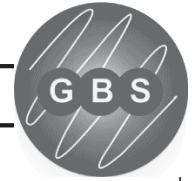
- Result:
- Negative for GBS
 - Positive for GBS
 - Not done
 - Unclear
 - Failed
 - No swab

Notes inc. reason for failure:

.....

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GBS Study Data Collection Form 3



FORM 3 to be sent to Microbiology with one pair of the Mother's swabs, Baby swab follows

Hospital Number: Study Number:
 Forename(s): Surname:
 Date of birth (dd-mon-yyyy):

If using hospital stickers, please ensure that all four data collection forms are given a sticker

MICROBIOLOGIST TO COMPLETE THE FOLLOWING

MOTHER VAGINAL SWAB CULTURE Date result available (dd-mon-yyyy):.....

Direct culture:

- Negative for GBS
- Positive for GBS
- Not done
- Unclear
- Failed
- No swab

Culture growth :

- No growth
- Light growth
- Moderate growth
- Heavy growth

Enrichment culture:

- Negative for GBS
- Positive for GBS
- Not done
- Unclear
- Failed
- No swab

Notes inc. reason for failure:

MOTHER RECTAL SWAB CULTURE Date result available (dd-mon-yyyy):.....

Direct culture:

- Negative for GBS
- Positive for GBS
- Not done
- Unclear
- Failed
- No swab

Culture growth :

- No growth
- Light growth
- Moderate growth
- Heavy growth

Enrichment culture:

- Negative for GBS
- Positive for GBS
- Not done
- Unclear
- Failed
- No swab

Notes inc. reason for failure:

BABY EAR SWAB CULTURE Date result available (dd-mon-yyyy):.....

Direct culture:

- Negative for GBS
- Positive for GBS
- Not done
- Unclear
- Failed
- No swab

Culture growth :

- No growth
- Light growth
- Moderate growth
- Heavy growth

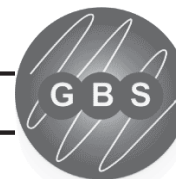
Enrichment culture:

- Negative for GBS
- Positive for GBS
- Not done
- Unclear
- Failed
- No swab

Notes inc. reason for failure:

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GBS Study Data Collection Form 4



FORM 4 for Community Midwife to complete and return to the GBS Study Collection Envelope

Hospital Number: Study Number:
 Forename(s): Surname:
 Date of birth (dd-mon-yyyy):

If using hospital stickers, please ensure that all four data collection forms are given a sticker

BABY DETAILS

Date form was completed (dd-mon-yyyy):

Sex: Male Female Birth weight (grams):

How many nights did baby spend in hospital? If > 7 nights, please specify the reason:

Did baby receive antibiotics within the first 7 days of life? No Yes If yes, please specify why:

Was the baby admitted to:

Postnatal ward	No <input type="checkbox"/>	Yes <input type="checkbox"/>
SCBU	No <input type="checkbox"/>	Yes <input type="checkbox"/>
Other ward	No <input type="checkbox"/>	Yes <input type="checkbox"/> If yes, please specify:

INFECTION DETAILS *(Record infections with onset in first 7 days of life)*

Infection? No Yes (if no please go to next section (Mother details), if yes please complete section below)

Invasive infection? No Yes If yes was infection:

Invasive with GBS? No Yes If yes, date of onset:

Invasive with another micro-organism? No Yes

If yes, was it: Bacteraemia Meningitis Other Date of onset:

Diagnosed clinically by a doctor? No Yes If yes, date of diagnosis:

Superficial Infection? No Yes If yes, was infection:

Superficial with GBS? No Yes If yes, date of onset:

Superficial with another micro-organism? No Yes If yes, date of onset:

Diagnosed clinically by a doctor? No Yes If yes, date of diagnosis:

MOTHER DETAILS *(Please record details of mother's postnatal care)*

How many nights did mother spend in hospital? If >7 nights, please specify the reason:

Date of Mother's discharge from hospital:

Was the Mother admitted to a:

Postnatal ward	No <input type="checkbox"/>	Yes <input type="checkbox"/>
ICU	No <input type="checkbox"/>	Yes <input type="checkbox"/>
General ward	No <input type="checkbox"/>	Yes <input type="checkbox"/>
Another ward	No <input type="checkbox"/>	Yes <input type="checkbox"/> Specify:

Return to: BCTU, GBS Study, FREEPOST MID21289, Park Grange, 1 Somerset Road, Birmingham B15 2BR



Acceptability Questionnaire for the Group-B Streptococcus Study

Form Identification

GBS Study No. _____

Mother's initials: _____

Date received: _____

Date entered: _____

We would like you to answer some questions for us on the study, your health and your baby's health. All your answers will be confidential and will not affect your treatment or your baby's treatment. In all the following questions GBS refers to Group-B streptococcus. Please tick the box which best represents your views.

Date this questionnaire was completed (dd-mon-yyyy): _____

1. Have you taken any painkillers in the last 24 hours? No Yes if yes, please tick **all** painkillers taken:
 Paracetamol / Ibuprofen / Codydramol / Cocodamol / Coproxamol Voltarol / Diclofenac
 Pethidine / Morphine / Oromorph Epidural / Spinal Entenox / Gas and air Don't know

Please tick only one box per question throughout the rest of the questionnaire

These first questions are about GBS and taking part in the study

How satisfied are you with the information you received from your midwife on the following:

	Very satisfied	Satisfied	Neither	Unsatisfied	Very unsatisfied
2 What GBS is?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3 What causes GBS infection in mothers?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4 How GBS is passed onto babies during labour?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5 Treatment for GBS during labour?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6 The benefits to you of treatment?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7 The benefits to your baby of you being treated before or during labour?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8 Possible side effects of treatment on you?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9 Possible side effects of treatment on your baby?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10 The research study?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11 What taking part involved?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Having samples taken

Only answer this section if you agreed to be swabbed. If you did not have swabs taken, please go to Q.24.

12 Overall how happy were you with the way the samples were taken?	Very happy	Happy	Neither	Unhappy	Very unhappy
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13 How comfortable did you feel when the vaginal sample was taken?	Very comfortable	Comfortable	Neither	Uncomfortable	Very uncomfortable
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14 How comfortable did you feel when the rectal sample was taken?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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- | | | Not at all
embarrassed | Slightly
embarrassed | Embarrassed | Very
embarrassed |
|----|-----------------------------------------------------------------|---------------------------|--------------------------|--------------------------|--------------------------|
| 15 | How embarrassed did you feel when the vaginal sample was taken? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 16 | How embarrassed did you feel when the rectal sample was taken? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

The following questions ask you about how you think you would feel about having this test done if it was part of normal care during labour (not part of a research study)

- | | | Very
confident | Confident | Neither | Unconfident | Very
unconfident |
|----|--------------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 17 | How confident are you that the results of the test could be kept confidential? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 18 | How confident are you that the test would be done properly? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 19 | How confident are you that you would be free to make a choice about treatment? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
-
- | | | Yes
definitely | Probably | Don't
know | Probably
not | Definitely
not |
|----|------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 20 | If the test showed that you had GBS, would you have felt happy to go ahead with treatment there and then? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 21 | Would you prefer not to have the test during labour, but just be treated if your doctor/midwife thought you should be? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 22 | Would you recommend the test to someone else? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
-
- | | | Very
important | Important | Neither | Unimportant | Very
unimportant |
|----|------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 23 | How important do you think it would be for you to have the test? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

The following questions ask you about your views on GBS

Views about you and GBS

On a scale of 1 to 10, please circle the number that best represents your views.

- 24 Do you think you would experience symptoms from GBS?
 No symptoms at all 0 1 2 3 4 5 6 7 8 9 10 Many severe symptoms
- 25 How concerned would you be about having GBS yourself?
 Not at all concerned 0 1 2 3 4 5 6 7 8 9 10 Extremely concerned
- 26 Please list in rank order the three most important factors you think causes GBS in pregnant women. The most important causes to me:
 1.
 2.
 3.

The next questions are about GBS and your baby

On a scale of 1 to 10, please circle the number that best represents your views.

- 27 How much would contracting GBS affect your baby's life?
 No effect at all 0 1 2 3 4 5 6 7 8 9 10 Severe effect
- 28 If your baby was ill with GBS, how long do you think the illness would last if not treated?
 A very short time 0 1 2 3 4 5 6 7 8 9 10 Forever
- 29 How much control do you feel you would have over GBS in your baby?
 Absolutely no control 0 1 2 3 4 5 6 7 8 9 10 Total control
- 30 How much do you think treatment after birth (antibiotics) could help if your baby had GBS?
 Not at all 0 1 2 3 4 5 6 7 8 9 10 Extremely helpful
- 31 Do you think your baby would experience symptoms from GBS?
 No symptoms at all 0 1 2 3 4 5 6 7 8 9 10 Many severe symptoms
- 32 How concerned would you be about your baby having GBS?
 Not concerned at all 0 1 2 3 4 5 6 7 8 9 10 Extremely concerned
- 33 How well do you feel you understand GBS in babies?
 Do not understand at all 0 1 2 3 4 5 6 7 8 9 10 Understand very clearly
- 34 How much does the risk of GBS in your baby affect you emotionally (e.g. does it make you angry, scared, upset or depressed)?
 Not at all affected emotionally 0 1 2 3 4 5 6 7 8 9 10 Extremely affected emotionally
- 35 Please list in rank order the three most important factors you think causes GBS in newly born babies.
 The most important causes to me:
 1.
 2.
 3.

These questions are about how you feel about yourself and your baby

First, your own health generally (not just at the moment)

- | | | Not at all | A little bit | Moderately | Quite a bit | A great deal |
|----|----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 36 | Do you ever think that there is something seriously wrong with your body? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 37 | Do you worry a lot about your health? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 38 | Is it hard for you to believe a doctor when they tell you there is nothing to worry about? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 39 | Do you often worry about the possibility that you have a serious illness? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 40 | Are you bothered by many different pains and aches? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 41 | If a disease is brought to your attention (e.g. on the TV, radio, newspapers or by someone you know) do you worry about getting it yourself? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 42 | Do you find you are bothered by many different symptoms? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

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Now, how you felt about your baby's health during pregnancy

	Not at all	A little bit	Moderately	Quite a bit	A great deal
43 Did you think there was something seriously wrong with your baby?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
44 Did you worry a lot about your baby's health?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
45 Was it hard for you to believe a doctor or midwife when they told you there was nothing to worry about?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
46 Did you often worry about the possibility that your baby had a serious condition?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
47 If a condition was brought to your attention did you worry about your baby having it?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
48 Did you have any tests done to check your baby's health before birth? e.g. tests for Down syndrome		No had no tests <input type="checkbox"/>	Yes had some tests <input type="checkbox"/>	Yes had all tests available <input type="checkbox"/>	Don't know <input type="checkbox"/>

A number of statements which people have used to describe themselves are given below. Tick the box to indicate how you feel right now, that is at this moment

	Not at all	Somewhat	Moderately so	Very much so
49 I feel calm	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
50 I am tense	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
51 I feel upset	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
52 I am relaxed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
53 I feel content	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
54 I am worried	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please use the space below to add any other comments you would like to make about the study, your and your baby's treatment or your and your baby's health

Thank you for answering these questions

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Appendix 10

National Screening Committee's criteria for appraising the viability, effectiveness and appropriateness of a screening programme

The criteria, which are set out below, are based on the classic criteria first promulgated in a World Health Organization report in 1966 but take into account both the more rigorous standards of evidence required to improve effectiveness and the greater concern about the adverse effects of health care; regrettably some people who undergo screening will suffer adverse effects without receiving benefit from the programme.

These criteria have been prepared taking into account international work on the appraisal of screening programmes, particularly that in Canada and the USA. It is recognised that not all of the criteria and questions raised in the format will be applicable to every proposed programme, but the more that are answered the more it will assist the National Screening Committee to make better evidence-based decisions.

All of the following criteria should be met before screening for a condition is initiated:

The condition

- The condition should be an important health problem.
- The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor or disease marker and a latent period or early symptomatic stage.
- All of the cost-effective primary prevention interventions should have been implemented as far as practicable.

The test

- There should be a simple, safe, precise and validated screening test.
- The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

- The test should be acceptable to the population.
- There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

The treatment

- There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
- There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
- Clinical management of the condition and patient outcomes should be optimised by all health-care providers before participation in a screening programme.

The screening programme

- There must be evidence from high-quality RCTs that the screening programme is effective in reducing mortality or morbidity.
- When screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (e.g. Down syndrome, cystic fibrosis carrier screening) there must be evidence from high-quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
- There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.
- The benefit from the screening programme should outweigh the physical and psychological

harm (caused by the test, diagnostic procedures and treatment).

- The opportunity cost of the screening programme (including testing, diagnosis, treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).
- There must be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.
- Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be made available before commencement of the screening programme.
- All other options for managing the condition should have been considered (e.g. improving treatment, providing other services) to ensure that no more cost-effective interventions could be introduced or current interventions increased within the resources available.
- Evidence-based information explaining the consequences of testing, investigation and treatment should be made available to potential participants to assist them in making an informed choice.
- Public pressure for widening the eligibility criteria for reducing the screening interval,

and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

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We look forward to hearing from you.