

Xpert GBS test for the intrapartum detection of group B streptococcus

Medtech innovation briefing

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Summary

The Xpert GBS test detects group B streptococcus (GBS) colonisation in pregnant women, using rectal and vaginal swabs. One randomised controlled trial reported a sensitivity of 89% and a reduction in intrapartum antibiotic prophylaxis. Seven diagnostic accuracy studies reported that Xpert GBS has good sensitivity. The Xpert GBS test is run on the GeneXpert molecular diagnostic system and each test costs £38.80.

In current NHS practice, antibiotic prophylaxis is offered based on clinical risk factors without routine testing. If a rapid and effective test to detect GBS colonisation were adopted, it could reduce use of broad-spectrum antibiotics in line with antibiotic stewardship guidelines.

<p>Product summary and likely place in therapy</p> <ul style="list-style-type: none"> • The Xpert GBS test is a rapid polymerase chain reaction (PCR) test for detecting group B streptococcus (GBS) colonisation in women who are about to give birth. • Guidelines from the Royal College of Obstetricians and Gynaecology and The National Screening Committee do not currently recommend routine screening for GBS at any stage during pregnancy. Additionally, NICE does not currently recommend selective testing for women considered to be at increased risk of GBS. • If a rapid and effective test to detect GBS colonisation were adopted, it could improve antibiotic stewardship. The Xpert GBS test could be used to identify GBS colonisation at the onset of labour as an adjunct to the risk factor based approach, and could potentially reduce the unnecessary use of intrapartum antibiotic prophylaxis. 	<p>Effectiveness and safety</p> <ul style="list-style-type: none"> • One randomised controlled trial (n=229) included 2 phases: phase 1 reported a sensitivity of 89%, and a reduction in intrapartum antibiotic prophylaxis based on Xpert GBS results, but there was a high rate of invalid results (44%). Phase 2 used an upgraded version of the test and reported that the level of invalid results reduced to 15% (statistically significant reduction $p < 0.001$). • One diagnostic accuracy and feasibility study (n=695) reported a sensitivity of 85%. Intrapartum antibiotic prophylaxis was possible for at least 4 hours in 73 of 107 women (68%) when based on the Xpert GBS test, compared with 68 of 107 women (64%) when based on antenatal bacterial cultures ($p = 0.54$). • Six diagnostic accuracy studies (n=55 to n=968) reported that Xpert GBS is a sensitive test that has the potential to help identify GBS colonisation in pregnant women. None investigated the impact of the test on antibiotic prescribing. • The version of Xpert GBS used in each of these diagnostic accuracy studies was not clear.
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Technical factors	Cost and resource use
<ul style="list-style-type: none"> The assay detects GBS from combined vaginal and rectal swab specimens and results are given in 50 minutes or less, compared with 24–48 hours for conventional bacterial culture techniques. 	<ul style="list-style-type: none"> The GeneXpert system is needed to run the Xpert GBS test. This costs between £17,602 and £118,119 depending on the module configurations. The individual test cartridges cost £38.80. No economic studies identified were generalisable to current NHS practice.

Introduction

Group B streptococcus (*Streptococcus agalactiae*; GBS) is a Gram positive bacterium that is one of the leading causes of infectious neonatal morbidity and mortality. The bacteria can colonise (be present without causing disease) the vaginal and gastrointestinal tracts in healthy women, and it has been estimated that approximately 14% of all women in the UK are carriers (Colbourn et al. 2007). During labour and birth, babies may come into contact with the bacteria in the birth canal and may themselves become colonised.

Although most babies are unaffected by GBS colonisation, a small number may develop clinical infection, known as early-onset GBS infection. Clinical infection typically happens within the first 12 hours of the baby's life, and the baby can become symptomatic between birth and 7 days of life. It is estimated that 1 in 2000 babies born in the UK and Ireland develop early onset GBS infection (UK National Screening Committee 2012). Consequently, approximately 340 of the 680,000 babies born in the UK each year are likely to develop early-onset GBS infection. The reasons why only some babies who are colonised with group B streptococcus go on to develop early-onset GBS infection are not well understood.

Most babies who develop a clinical GBS infection are successfully treated and make a full recovery. However, despite good medical care the infection can go on to cause life-threatening complications such as septicaemia, pneumonia and meningitis. Mortality among babies with early-onset clinical GBS infection is 10–30%, with the highest risk in premature babies (Mueller et al. 2014). One in 5 babies who survive the infection will be permanently affected and may have problems such as cerebral palsy, blindness, deafness and serious learning difficulties (NHS Choices 2013). For every woman with GBS

colonisation during birth, the risk to their baby of neonatal death from early-onset GBS neonatal sepsis is 0.03% (UK National Screening Committee 2012).

Currently, the Royal College of Obstetricians and Gynaecologists (RCOG) does not recommend routine screening or testing for GBS colonisation in pregnant women in the UK, because the clinical and cost effectiveness of this strategy remains unclear (RCOG 2012). Similarly, the National Screening Committee does not recommend routine testing or screening for GBS at any stage during pregnancy (UK National Screening Committee 2012). In addition, NICE guidelines on [antibiotics for early-onset neonatal infection](#) and [intrapartum care](#) do not recommend selective testing for GBS in women considered to be at increased risk of GBS transmission.

Intrapartum antibiotic prophylaxis of pregnant women is believed to reduce the incidence of early onset GBS infection in babies, although there is a lack of robust evidence to demonstrate this (Ohlsson and Shah, 2014). It is thought that the optimal antibiotic regimen to prevent GBS transmission is 2–4 hours of intrapartum antibiotic prophylaxis, for example, with benzylpenicillin or clindamycin (RCOG 2012).

GBS may be detected incidentally during the early stages of pregnancy from a routine urine test indicating signs of an infection (bacteriuria). Microbiological techniques such as standard direct plating or enriched culture medium plates are then used to identify the bacteria.

Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings.

About the technology

CE marking

The Xpert GBS test is classed as an in vitro diagnostic device. The manufacturer, Cepheid, received the first CE mark for the device in March 2006. The most recent renewal was in October 2010.

Description

The Cepheid Xpert GBS test is a qualitative in vitro diagnostic test to detect GBS colonisation in women during childbirth. The test is designed for use at the point of care in labour wards, or in clinical laboratories, and is run on the GeneXpert molecular diagnostic system. The test identifies GBS DNA from combined vaginal and rectal swab specimens, using fully automated real-time polymerase chain reaction (PCR) with fluorogenic detection of the amplified DNA. Test results are available in 50 minutes or less.

Each test kit comprises a transport container that has 2 swabs attached to the lid of the container. The swabs are used to take 2 identical combined rectal and vaginal samples, which are then processed differently. The 2 swabs are inserted into the woman's vagina, to collect samples of the secretions from the mucosa of the lower third of the vagina. The same swabs are then each inserted approximately 2.5 cm beyond the anal sphincter to collect the rectal samples. The swabs are then returned to the transport container. Only one swab is needed for Xpert GBS testing. The second swab can be used for antimicrobial susceptibility testing for women who are GBS positive but who have a penicillin allergy. The samples should be analysed immediately, and must be refrigerated if not processed within 24 hours.

The Xpert GBS test is run using the Cepheid clinical in vitro diagnostic system, consisting of 3 main components:

- The GeneXpert molecular diagnostic system. This is available in 4 configurations (I, II, IV or XVI) consisting of 1, 2, 4 or 16 modules, and a larger Infinity version with 16 to 80 modules. Point of care testing is more suited to the smaller 1 or 2 module versions; the larger 4 and 80 module configurations are more suitable for clinical laboratory use. Each module is loaded with 1 Xpert GBS test cartridge per person. Multi-module versions can run several, independent tests using different test cartridges at any time.
- A computer system, which is supplied with the GeneXpert system, to run the GeneXpert DX software and store a results database. The software is used to select test definitions, to monitor the automated test process, and to view, print and export the results and generate reports. A cartridge barcode scanner is included to facilitate data entry.

- The single-use Xpert GBS cartridge. The Xpert test cartridge is self-contained and holds pre-packaged freeze-dried PCR reagent beads. The cartridge holds the PCR reaction in an integrated reaction tube. There are 3 automated quality control samples in each cartridge: a probe check control, an internal control and a sample processing control.

Each Xpert GBS cartridge consists of several internal processing chambers to hold the original sample, PCR reagents, the processed sample and waste solutions. The Xpert GBS test swab is inserted into the sample chamber of the cartridge and the swab tip is broken off. The cartridge is loaded into a system module, and GBS test processing and analysis starts automatically by closing the module door.

The manufacturer also supplies a range of cartridges for 18 other in vitro diagnostic tests including methicillin-resistant *Staphylococcus aureus* (Xpert MRSA), influenza (Xpert Flu) and *Chlamydia trachomatis* (Xpert CT). These tests are beyond the scope of this briefing.

Additional accessories available for the GeneXpert system include 16 or 32 cartridge trays, a colour laser printer with USB cable and an uninterruptible power supply.

Results are analysed by the GeneXpert software from measured fluorescent signals, using calculation algorithms. Positive results are reported in approximately 35 minutes and negative results confirmed in approximately 50 minutes.

Intended use

The Xpert GBS test is designed for the rapid identification of antepartum and intrapartum GBS colonisation, via clinical laboratory testing or point of care in the labour ward. Antepartum testing is beyond the scope of this briefing.

Setting and intended user

The Xpert GBS test and GeneXpert system can be used in secondary care maternity wards or delivery units. In these settings, the system would be operated by midwives and nursing staff, who would know about GBS risks and have received appropriate training on the Xpert GBS test with the GeneXpert system.

The Xpert GBS test could also be used in clinical laboratories, where it would be used by laboratory staff.

Current NHS options

There is currently no routine testing for GBS colonisation at any stage of pregnancy. Selective testing for GBS colonisation in women who are at high risk of GBS transmission is not recommended in NICE's guidelines on [antibiotics for early-onset neonatal infection](#) or on [intrapartum care](#). Diagnosis of GBS infection is typically incidental after detecting an infection from routine urine testing during pregnancy.

At present, a risk-factor approach is used in the NHS. The RCOG guidelines (2012) recommend that women who are at increased risk for transmission of GBS are given intrapartum antibiotic prophylaxis during labour to prevent colonisation of the baby. These are women who:

- have previously had a baby with clinical GBS infection
- have had a vaginal swab for GBS during their current pregnancy when there had been a clinical indication of infection
- have had GBS bacteriuria during their current pregnancy.

The following indications are also considered for offering broad-spectrum antibiotics, which should include activity against GBS:

- intrapartum fever (pyrexia >38°C)
- intra-amniotic infection (chorioamnionitis).

For women in these groups, the RCOG (2012) guidelines recommend that 3 g intravenous benzylpenicillin should be given as soon as possible after the onset of labour and then 1.5 g given 4-hourly until delivery. Women with an allergy to benzylpenicillin should have 900 mg of clindamycin intravenously every 8 hours.

NICE is not aware of other CE marked devices that have a similar function to the Xpert GBS test for the rapid detection of GBS in women during labour.

Costs and use of the technology

The Xpert GBS system consists of several essential components and optional accessories. List prices (excluding VAT) for the essential components are as follows:

- the GeneXpert molecular diagnostic system (1–16 modules) including computer system costs from £17,602 for a single-module system to £118,119 for a 16-module system
- the Xpert GBS cartridge costs £38.80 per single test
- sample collection device (transport container with dual swab) costs £37 per pack of 50.

List prices for optional accessories (excluding VAT) are:

- uninterruptible power supply for GeneXpert: £1,522
- laser printer with USB cable: £110
- GeneXpert 16-cartridge tray: £8
- GeneXpert 32-cartridge tray: £12.

Training is given by the manufacturer during installation and is free of charge. This includes training in sample collection, preparing the cartridge(s) and analysing results. Training takes about 30 minutes and additional training materials are provided to staff. Refresher training is available on request and is also free of charge.

The GeneXpert system has an anticipated lifespan of over 10 years. The manufacturer offers annual maintenance contracts ranging from £2,103 to £7,107 depending on the number of modules in the system. The annual service includes preventative maintenance and module calibration, and on-site and telephone technical support are available.

Likely place in therapy

Although not currently recommended in NICE guidelines, the Xpert GBS test is designed for use at the onset of labour to test for GBS colonisation in women at increased risk of carrying GBS, with the aim of reducing unnecessary intrapartum antibiotic prophylaxis in high-risk women who are not colonised. This would support current initiatives to improve antibiotic stewardship in the NHS.

Specialist commentator comments

One specialist commentator highlighted that the Xpert GBS test would be of some value to

women who are at increased risk for transmission of GBS. Confirmation of a negative result for GBS would avoid both unnecessary venous cannulation and the use of intrapartum antibiotic prophylaxis for these women. Also, it would allow these women a greater choice of options for giving birth, such as labour in water or homebirth. However, this commentator noted that the benefits of testing would be limited. Because babies of women with confirmed GBS colonisation are usually only observed for 12 hours after birth, it was unlikely that testing would shorten the length of hospital stay.

Two specialist commentators indicated that the reduction of intrapartum antibiotic prophylaxis may be limited to 3 of the 5 high-risk groups because women with maternal pyrexia or recognised chorioamnionitis would always be given broad spectrum antibiotics at the onset of labour within 1 hour. Similarly, women who had previously had a baby with a GBS infection would be given antibiotics regardless of the GBS test result. A third commentator further highlighted that regardless of GBS status and the result of testing, a woman considered to be at increased risk of GBS transmission would still receive intrapartum antibiotic prophylaxis.

One commentator indicated that midwives would require full training for adoption of the technology and that it would require significant financial commitment from NHS trusts that do not currently carry out screening. One commentator highlighted that the system would be operated by midwives or nursing staff with additional support from a hospital point-of-care team. Appropriate internal quality control and external quality assessment monitoring would be needed.

Equality considerations

NICE is committed to promoting equality and eliminating unlawful discrimination. In producing guidance, NICE aims to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women
- eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

The Xpert GBS test is intended for use in pregnant women during labour. Sex and

pregnancy are protected characteristics under the Equality Act (2010).

Patient and carer perspective

The patient organisation Group B Streptococcus Support provided the following commentary on a draft version of the briefing:

- Some babies are at increased risk of GBS infection, including babies of women in preterm labour, and women with prolonged rupture of membranes.
- A rapid bedside test would potentially enable the GBS status of these women to be identified more quickly than using conventional culture techniques.

Evidence review

Clinical and technical evidence

Regulatory bodies

A search of the Medicines and Healthcare Products Regulatory Agency (MHRA) website revealed no manufacturer Field Safety Notices or Medical Device Alerts for this device. No reports of adverse events were identified from a search of the US Food and Drug Administration (FDA) database: Manufacturer and User Device Facility Experience (MAUDE).

Clinical evidence

There is a substantial body of published evidence describing the use of the Xpert GBS test for intrapartum identification of GBS. A literature search identified 10 fully published studies on the Xpert GBS. Two diagnostic accuracy studies were excluded because they did not include a suitable reference standard. This briefing focuses on 1 randomised controlled trial and 1 diagnostic accuracy study, which investigated the feasibility of using intrapartum antibiotic prophylaxis based on the results of polymerase chain reaction (PCR) testing. The results of 6 further diagnostic accuracy studies are also summarised.

The randomised controlled trial by Hakansson et al. (2014) had 2 phases. The first phase

used an earlier version of the Xpert GBS test system (when reagents were added manually by the user); however, an upgraded version was used during the second phase of the study and this is likely to be the current Xpert GBS system. The first phase was a multicentre randomised controlled trial that primarily aimed to determine whether introducing the Xpert GBS test into a labour ward could direct appropriate use of prophylactic antibiotics in women considered to be at increased risk of carrying GBS. A secondary aim was to evaluate the efficacy of intrapartum antibiotic prophylaxis to prevent GBS colonisation in the baby. During this phase, 229 women across 6 delivery units in Sweden were randomised into 2 groups: 112 to group A and 117 to group B. Group A were swabbed for both Xpert GBS PCR (using the older version of the device) and conventional bacterial culture, and intrapartum antibiotic prophylaxis was administered if the PCR assay result was positive or invalid for GBS. Group B were swabbed for conventional bacterial culture only and were treated with intrapartum antibiotic prophylaxis according to the Swedish recommended guidelines, which advocate a risk-based approach. In both groups, the babies were swabbed for conventional culture to determine their GBS colonisation status.

The second phase was non-randomised and aimed to evaluate the performance of an upgraded version of the Xpert GBS test in 94 women across 3 of the 6 centres from the first phase. All of the women were tested for GBS using both Xpert GBS PCR (using the upgraded version of the device) and conventional bacterial culture. Intrapartum antibiotic prophylaxis was administered if the PCR result was either positive or invalid.

The results of phase 1 reported that the sensitivity and specificity of the Xpert GBS test when conclusive were 89% and 90% respectively, when compared with bacterial culture as the reference standard. However, the Xpert GBS PCR assay results were invalid in 44% (47/106) of cases with complete data (6 test results were reported missing). The authors reported a statistically significant 39% reduction in the use of intrapartum antibiotic prophylaxis in this phase ($p < 0.001$), from 92% (107/117) in the recommended guideline group to 53% (59/112) in the PCR group.

The results of phase 2 showed a reduction in the proportion of invalid results to 15% (14/94) using the upgraded system. There was also a further reduction of intrapartum antibiotic prophylaxis administration in phase 2, from 53% of women (59/112) using the earlier version of Xpert GBS to 33% of women (31/94) using the upgraded system.

The authors concluded that the Xpert GBS test was a promising tool for improving intrapartum antibiotic prophylaxis, which would allow a significant reduction in the use of

these antibiotics. A description of the study and its results are included in table 1.

Table 1 Summary of the Hakansson et al. (2014) randomised controlled trial

Phase 1 – Randomised			
	Group 1A – Xpert GBS PCR + conventional culture	Group 1B – conventional culture + recommended guidelines (Control arm)	Analysis (chi squared test or Fisher's exact test)
Randomised	n=112	n=117	
Efficacy	Not reported	Not reported	
Primary outcome: Use of IAP	53% (59/112)	92% (107/117)	p<0.001
Secondary outcomes: Efficacy of IAP (based on culture) to prevent GBS colonisation in the baby	IAP given for a duration of at least 2 hours = 5/43 GBS positive infants (12%) 32 of these 43 women were given IAP for at least 4 hours = 4/32 GBS positive infants (13%)		No p value recorded
Secondary outcomes: Sensitivity analysis of PCR compared with culture	Sensitivity: 89% Specificity: 90%	Control arm	
Phase 2 – Non-randomised (n=94)			
	Phase 1 data (original Xpert GBS PCR assay)	Phase 2 data (upgraded Xpert GBS PCR assay)	
Primary outcome: Invalid PCR result	44% (47/106)	15% (14/94)	p<0.001

Secondary outcome: Use of IAP	53% (59/112)	33% (31/94)	p<0.01, OR 0.44 (95% CI 0.24–0.81).
Safety	None reported	None reported	
Patients reporting serious adverse events	None reported	None reported	
Abbreviations: CI, confidence interval; GBS, group B streptococcus; IAP, intrapartum antibiotic prophylaxis; n, number of patients; OR, odds ratio; PCR, polymerase chain reaction			

The diagnostic accuracy and feasibility study by de Tejada et al. (2011) was conducted in the labour ward of a hospital in Switzerland. A run-in phase was carried out over 1 month to train the midwives to perform the Xpert GBS PCR assay on the GeneXpert system; this phase included 132 women. A further 563 women were included in the second phase of the study, resulting in a total of 695 women included for the diagnostic accuracy study. The feasibility of intrapartum testing to guide intrapartum antibiotic prophylaxis was evaluated using only the results from the second phase of the study, and included 557 women. The women included in this study were not considered to be at increased risk of GBS and were excluded if they had previously had a baby with GBS sepsis, or a positive urinary culture for GBS during pregnancy.

The study compared the results for each patient from an intrapartum Xpert GBS PCR test and antenatal bacterial culture with the results from an intrapartum bacterial culture, which was considered the reference standard. The samples used for both the bacterial cultures were from rectovaginal swabs. The sensitivities of the intrapartum Xpert GBS PCR and antenatal culture were recorded as 85.0% and 81.0% respectively. The proportion of invalid results from the Xpert GBS test was 8.4% (58/695). The authors did not report specificities of the tests because they stated that if culture is used as the reference standard, those patients considered to be false positive by PCR could in fact be positive for GBS, because the PCR assay may be more specific than culture. The feasibility study showed that 4 or more hours of intrapartum antibiotic prophylaxis could be given to 68.2% (73/107) of women whose PCR results were positive for GBS, compared with 63.6% (68/107) women whose antenatal culture results were positive for GBS (p=0.54). The intrapartum PCR assay correctly identified GBS colonisation status in 74.4% (32/43) of women who were delivering pre-term. Of these 32 women, antenatal culture only correctly identified GBS status in 31.3% (10/32).

The authors concluded that intrapartum GBS testing is feasible and is at least as accurate as antenatal testing, but did not state whether Xpert GBS testing had any benefit over conventional bacterial culture. A description of the study and its results are included in table 2.

Table 2 Summary of the de Tejada et al. (2011) diagnostic accuracy and feasibility study

Study component	Description
Objectives/ hypotheses	<p>Primary objective: to evaluate the diagnostic accuracy of the intrapartum PCR using the Xpert GBS system and antenatal culture (at 35–37 weeks) compared with the results of intrapartum culture.</p> <p>Secondary objective: to investigate the feasibility of implementing intrapartum antibiotic prophylaxis based on the results of the intrapartum PCR.</p>
Study design	<p>Prospective diagnostic accuracy study</p> <p>A run-in phase was performed between December 2007 and January 2008 to train the midwives to perform the PCR assay on the GeneXpert system. Women were recruited in this phase provided they met the eligibility criteria. During the second phase, from January to April 2008, all women delivering in the labour ward were included, provided they met the same eligibility criteria.</p> <p>During the feasibility study, only results from the second period were used.</p>
Setting	<p>Labour ward in the University Hospital of Geneva, Switzerland.</p> <p>Women were recruited in this phase if they met the eligibility criteria. During the second phase, from January to April 2008, all women delivering in the labour ward were included, if they met the same eligibility criteria.</p> <p>During the feasibility study, only results from the second period were used.</p>

Inclusion/ exclusion criteria	<p>Inclusion criteria: women considered not to be at risk of GBS colonisation.</p> <p>Exclusion criteria: elective caesarean section, a previous infant with GBS sepsis or a positive urinary culture for GBS during pregnancy.</p>
Primary outcomes	<p>Diagnostic accuracy of intrapartum PCR</p> <p>Feasibility of implementing IAP</p>
Statistical methods	<p>A power analysis calculated that 700 women would be needed to recruit 140 GBS culture-positive women and to show a statistically significant increase in assay sensitivity between antenatal culture and intrapartum PCR testing (alpha = 0.05 and power = 90%).</p> <p>McNemar's test was applied to estimate the sensitivity with a 95% confidence interval for the diagnostic accuracy study.</p> <p>Differences in proportions and continuous variables were analysed using Fisher's exact test and student t-test, respectively.</p> <p>A significance level of $p < 0.05$ was used.</p>
Participants	<p>n=695 women for the diagnostic accuracy study</p> <p>n=557 women for the feasibility study (a subset of the 695)</p>

Results	<p>Diagnostic accuracy of intrapartum Xpert GBS PCR:</p> <p>Colonisation rate:</p> <ul style="list-style-type: none"> • intrapartum culture = 19.3% (134/695) • intrapartum PCR = 19.8% (126/637) • antenatal culture = 19.6% (123/629) <p>Of the 695 women in the study, 66 antenatal cultures were not done, and in 58, no result was obtained from the intrapartum PCR after 2 attempts.</p> <p>Sensitivity (reference standard: intrapartum culture):</p> <ul style="list-style-type: none"> • intrapartum PCR = 85.0% (95% CI, 77.4–90.5) • antenatal culture = 81.0% (95% CI, 72.6–87.3) <p>The proportion of indeterminate test results from the intrapartum PCR was 8.4% (58/695).</p> <p>There were discordant results between antenatal culture and intrapartum culture in 6.9% (48/695) women. PCR was unable to resolve the result in 5 cases and was in agreement with the intrapartum culture in 62.8% (27/43) of the remaining women.</p> <p>Feasibility of implementing IAP:</p> <p>In 76.5% (426/557) of women, the results of the PCR were obtained at least 4 hours before delivery. Intrapartum antibiotic prophylaxis was administered to 26.0% (145/557) of women, 83.4% (121/145) for early onset GBS disease. Of these 121 women, 71.1% (86/121) received IAP for at least 4 hours.</p> <p>Intrapartum culture identified 107 GBS colonised women. In 68.2% (73/107) of these women, administration of IAP was feasible for at least 4 hours when based on PCR, and in 63.6% (68/107) when based on antenatal cultures (p=0.54).</p> <p>Nine of 43 women delivering pre-term were identified as colonised with GBS. Intrapartum PCR correctly identified GBS status at least 4 hours before delivery in 74.4% (32/43) and antenatal culture correctly identified GBS status in 31.3% (10/32) of these women.</p>
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Conclusions	The authors concluded that the sensitivity of the intrapartum PCR using Xpert GBS to detect GBS during labour was slightly superior to antenatal culture techniques; however, the difference was not statistically significant. The intrapartum approach would therefore allow the identification of high-risk groups for neonatal sepsis, such as women who are delivering pre-term, or women who were not followed throughout their pregnancy.
Abbreviations: CI, confidence interval; GBS, group B streptococcus; IAP, intrapartum antibiotic prophylaxis; n, number of patients; PCR, polymerase chain reaction	

Six other diagnostic accuracy studies reporting performance characteristics of the Xpert GBS test against a reference standard were identified. Each of these studies explicitly described the characteristics of the Xpert GBS test; however, it is not clear from the reports whether each study used the current version of the Xpert GBS test. Sensitivity rates ranged from 83.3% to 98.5% and indeterminate result rates ranged from 2.1% to 23.5%. These studies are briefly summarised in table 3.

Table 3 Brief summary of 6 additional Xpert GBS diagnostic accuracy studies

Reference	Study aims	Setting, number of patients and study dates	Selected results and conclusions

<p>Tanaka et al. (2015)</p>	<p>To analyse the diagnostic accuracy of the Xpert GBS assay for identification of group B streptococcus, using intrapartum culture as the reference standard.</p>	<p>Hospital in Japan n=79 Japanese women January - May 2014</p>	<p>Results were obtained for 73 women. The performance characteristics of the Xpert GBS assay compared with conventional culture were:</p> <ul style="list-style-type: none"> • sensitivity: 83.3% (95% CI 51.6–97.9) • specificity: 98.4% (95% CI 91.2–100.0) • PPV: 90.9% (95% CI 58.7–99.8) • NPV: 96.8 (95% CI 88.8–99.6). <p>Proportion of indeterminate results: not reported.</p> <p>The authors concluded that intrapartum real-time PCR for GBS screening has a similar accuracy to the antepartum conventional culture technique.</p>
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<p>Mueller et al. (2014)</p>	<p>To compare the Xpert GBS assay performed in the laboratory and in the labour ward, using selective culture as a reference standard.</p>	<p>Hospital in Switzerland n=300 women, (150 for phase I and 150 for phase II) January 2007 – August 2010</p>	<p>Phase I – swabs were analysed by selective culture and the Xpert GBS assay in the laboratory. Performance characteristics of the rapid PCR were:</p> <ul style="list-style-type: none"> • sensitivity: 85.7% • specificity: 95.9% • proportion of indeterminate results: 8.5%. <p>Phase II – swabs were analysed by selective culture and the Xpert GBS assay in the labour ward. Performance characteristics of the rapid PCR were:</p> <ul style="list-style-type: none"> • sensitivity: 85.7% • specificity: 95.7% • proportion of indeterminate results: 23.5%. <p>After initiating a 2 hour training period for operating personnel in the labour ward, the proportion of indeterminate results decreased to 13.4%.</p> <p>The authors concluded that the Xpert GBS assay in the labour ward yields adequate results to identify GBS colonisation; however, a short training period would be necessary to reduce the number of indeterminate results.</p>
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<p>Abdelazim (2013)</p>	<p>To compare the Xpert GBS assay with the standard antepartum culture for detecting group B streptococcus colonisation.</p>	<p>Hospital in Kuwait n=445 women Study dates not reported</p>	<p>The sensitivity and specificity of the Xpert GBS assay to diagnose GBS colonisation were 98.3% and 99.0% respectively, compared with 73% sensitivity and 95.5% specificity for antepartum culture ($p>0.05$). The accuracy of the intrapartum PCR test was 98.8% for detecting GBS colonisation in comparison to 90.0% for antepartum culture.</p> <p>Proportion of indeterminate results: 4.5%</p> <p>The authors concluded that the Xpert GBS assay is an accurate test when used at the bedside and has the potential to be used as a screening test for GBS colonisation to allow for appropriate management.</p>
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<p>Young et al. (2011)</p>	<p>To evaluate the Xpert GBS assay for detecting group B streptococcus.</p>	<p>Labour unit in a US medical centre n=559 women January – June 2010</p>	<p>The prevalence of GBS was 19.5% by antepartum culture and 23.8% by intrapartum culture.</p> <p>The performance characteristics of the Xpert GBS assay (using intrapartum culture as the reference standard) were:</p> <ul style="list-style-type: none"> • sensitivity: 90.8% (84.6–95.2%) • specificity: 97.6% (95.6–98.8%) • PPV: 92.3% (86.2–96.2%) • NPV: 97.1 (95.0–98.5%). <p>Proportion of indeterminate results: 2.1%.</p> <p>The performance characteristics of antepartum culture (using intrapartum as a reference standard) were:</p> <ul style="list-style-type: none"> • sensitivity: 69.2 (60.6–76.9%) • specificity: 96.0% (93.7–97.7%). <p>The authors concluded that the Xpert GBS assay may be superior to antepartum culture for detecting intrapartum GBS which could allow for more accurate management of labour and reduce the incidence of neonatal GBS sepsis.</p>
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<p>El Helali et al. (2009)</p>	<p>To evaluate the diagnostic accuracy of the Xpert GBS assay at the onset of labour using intrapartum culture as a reference standard and also compare it with screening by culture at 35–37 weeks gestation.</p>	<p>Maternity ward in a hospital in France n=968 April 2007 – March 2008</p>	<p>Using intrapartum culture as the reference standard, the performance characteristics of the Xpert GBS assay were:</p> <ul style="list-style-type: none"> • sensitivity: 98.5% • specificity: 99.6% • PPV: 97.8% • NPV: 99.7% • proportion of indeterminate results: 10.8%. <p>The authors concluded that the Xpert GBS assay is a highly accurate test that is able to determine intrapartum GBS status at point of care. The technology could improve the use of intrapartum antibiotic prophylaxis, including in women with pre-term labour or pre-term rupture of the membranes.</p>
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<p>Gavino and Wang (2007)</p>	<p>To evaluate the Xpert GBS assay for detecting GBS in active labour in the delivery unit.</p>	<p>Delivery unit of a hospital in the USA n=55 women Study dates not reported</p>	<p>Performance of the Xpert GBS assay was analysed using intrapartum culture results as the reference standard. The performance characteristics of the Xpert GBS assay were:</p> <ul style="list-style-type: none"> • sensitivity: 95.8% (95% CI 76.9–99.8) • specificity: 64.5% (95% CI 45.4–80.2) • PPV: 95.2% • NPV: 95.2% • positive likelihood ratio: 2.7 • negative likelihood ratio: 0.065. <p>Proportion of indeterminate results: not reported.</p> <p>The authors concluded that the Xpert GBS assay was highly sensitive for GBS detection in the sample population they had tested. However, corroboration of these data would be needed in a large population.</p>
<p>Abbreviations: CI, confidence intervals; GBS, group B streptococcus; n, number; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value</p>			

Recent and ongoing studies

One ongoing or in-development trial of Xpert GBS was identified in the preparation of this briefing:

- Group B Streptococcus (GBS) Polymerase Chain Reaction (PCR) Concordance Study ([NCT00972894](https://www.clinicaltrials.gov/ct2/show/study/NCT00972894)) – The manufacturer has stated that this trial is independent from Cepheid but the current status is unknown.

Costs and resource consequences

The Xpert GBS assay could be used as an intrapartum test for women considered to be at increased risk for transmission of GBS to their baby. As it does not replace an existing test, it would represent an additional acquisition cost to the NHS. However, resource-use savings could potentially be made through the offset of staff time and by costs avoided because of a reduction in unnecessary intravenous antibiotics and potential associated complications.

Two studies were identified that investigated the cost-effectiveness of different intra-partum screening approaches.

A Health Technology Assessment set in 2 large UK obstetric units investigated the cost effectiveness of rapid testing for GBS in women during labour (Daniels et al. 2009). The study comprised 2 parts: a diagnostic accuracy study to establish the efficacy of the Cepheid Smart GBS system (a precursor to the present Xpert GBS system) and an optical immunoassay; both were individually compared with a bacterial culture reference test. A decision analytic model was created to assess the cost effectiveness of the technologies in various scenarios. The study found that the Smart GBS system had better diagnostic accuracy than the optical immunoassay, although neither technique was cost-effective for managing high risk of colonisation in women during labour. The most cost-effective option was providing intravenous antibiotic prophylaxis for all women, without screening.

The costs of implementing intrapartum PCR screening for GBS, using the Xpert GBS assay in pregnant women, were compared with the previously used antenatal culture in a study by El Helali et al. (2012). The authors concluded that the newer PCR screening method provided superior diagnostic sensitivity, and that there was a greater than 50% chance that PCR dominated antenatal culture (was more effective and less expensive).

Strengths and limitations of the evidence

There is a reasonably large evidence base for using Xpert GBS for intrapartum identification of GBS. The evidence for this technology is primarily in the form of

diagnostic accuracy studies that focus on the diagnostic performance characteristics of the test, and most did not investigate the potential changes to clinical practice. This briefing has focused on 1 randomised controlled trial (Hakansson et al. 2014) and 1 diagnostic accuracy study (de Tejada et al. 2011) which described outcomes that could impact on the NHS.

The main limitation of the Hakansson et al. (2014) study was that the first phase involved a randomised controlled trial of an earlier version of the Xpert GBS test. This may have caused the high number of test results that were invalid in this phase of the study (44%). The authors reported a reduction in invalid results to 15% during the second phase of the study when an upgraded version of the Xpert GBS test, likely to be the current version, was evaluated. A large number of women were excluded for not fulfilling the eligibility criteria (106/335), which opens up the possibility of selection bias and may limit the generalisability of the study. The randomisation in this study appears to have been effective because both groups indicated similar numbers of each obstetric risk factor. The study does not appear to have been blinded to the researchers, clinicians, or participants. However, this is unlikely to have introduced significant bias because of the objective nature of the outcomes reported. The primary eligibility criteria were set to include all women in labour, who had at least 1 of the selected obstetric risk factors for GBS, but these were not the same as the risk factors used in the UK and this introduces issues of generalisability. The diagnostic analyses in this study were poorly reported, and were not replicable by the authors of this briefing, introducing the possibility of mistakes in the calculations.

Of the 7 diagnostic accuracy studies identified, the study by de Tejada et al. (2011) was the only one to assess the feasibility of implementing intrapartum antibiotic prophylaxis based on the results of the intrapartum PCR to detect GBS, using the Xpert GBS system. However, in this study healthy women in labour were screened for GBS, and the exclusion criteria included 2 obstetric risk factors for GBS colonisation, and therefore may not be generalisable to current NHS practice. A strength of the study was that the researchers included a large number of participants for both the diagnostic accuracy study and the feasibility study (695 and 557 respectively), which was based on a suitable power calculation to determine sample size. It is not clear whether the midwifery staff were blinded to the results of the antenatal culture before performing the intrapartum Xpert GBS PCR test, giving rise to potential bias, although this should be minimal as only objective outcomes were reported.

The remaining 6 diagnostic accuracy studies did not describe the potential impact or

feasibility of Xpert GBS testing at the point of care, or the potential clinical and resource implications of this. The range of sensitivity rates and indeterminate result rates reported in these studies may be because of different versions of the Xpert GBS test and different culture methods used as the reference standard. The studies were also done in various international hospital settings, therefore results and indications may not be generalisable to NHS practice.

The Health Technology Assessment by Daniels et al. (2009) should be considered with caution because it used a different version of the technology, with statistically significantly worse diagnostic accuracy than has since been reported for the current Xpert GBS system.

The cost-effectiveness study by El Helali et al. (2012) compared screening techniques and because it did not include consideration of treatment using a risk stratification algorithm, it is not generalisable to the NHS. This study was a 'before and after' study that did not feature a control arm or reference standard, and accordingly the results may be subject to significant bias. Additionally, the study was done in France and costs were reported in US dollars, further limiting generalisability.

Relevance to NICE guidance programmes

NICE has issued the following guidance:

- [Intrapartum care](#) (2014) NICE guideline CG190
- [Antibiotics for early-onset neonatal infection](#) (2012) NICE guideline CG149
- [Bacterial meningitis and meningococcal septicaemia](#) (2010) NICE guideline CG102
- [Intrapartum care](#) (last updated 2014) NICE pathway
- [Antenatal care](#) (last updated 2014) NICE pathway
- [Induction of labour](#) (last updated 2014) NICE pathway

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Search strategy and evidence selection

Search strategy

The search strategy was designed to identify evidence on the clinical and cost effectiveness of the Xpert GBS assay for direct intrapartum screening in labour or delivery.

The strategy was developed for MEDLINE (Ovid interface). The strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The search terms were identified through discussion within the research team, scanning background literature, browsing database thesauri and use of the PubMed [PubReminer tool](#). The strategy reflected the nature of the Medtech innovation briefing assessments as rapid evidence reviews.

The search comprised 3 concepts:

1) setting (pregnancy / labour / neonatal health);

2) group B streptococcus;

3) polymerase chain reaction.

Additional search lines on brand name, and manufacturer name combined with GBS terms, were also used. These lines were designed to capture any records that may have been missed by the 3 concept approach.

The strategy excluded non-English language publications. Animal studies were also excluded using a standard algorithm. No additional filters for study design were applied. The results were limited to studies added to the database from 2005 to January 2015, this reflected the date when the device was introduced (2006).

The final MEDLINE strategy was peer-reviewed by an independent information specialist. The MEDLINE strategy was translated appropriately for the other databases searched. The PubMed search was limited to records that were not fully indexed on MEDLINE.

The following databases were searched:

- Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley)
- Cochrane Database of Systematic Reviews (Cochrane Library, Wiley)
- Database of Abstracts of Reviews of Effects (Cochrane Library, Wiley)
- Embase (Ovid SP)
- Health Technology Assessment Database (Cochrane Library, Wiley)
- MEDLINE and MEDLINE in Process (Ovid SP)
- NHS Economic Evaluation Database (Cochrane Library, Wiley)
- [PubMed](#)

Evidence selection

A total of 419 records were retrieved from the literature search. After de-duplication, 265 records remained and were sifted against the inclusion criteria at title and abstract level.

Records were sifted independently by 2 researchers. Any disagreements were discussed and agreement was reached in all cases, so a third independent arbiter was not required. The first sift removed 237 records based on the following exclusion criteria:

- articles of poor relevance against search terms
- publication types that were out of scope
- non-English language studies
- conference abstracts
- review articles.

Full articles were retrieved for 28 of the remaining studies. Full text assessment was done independently by 2 researchers to identify relevant primary research addressing the key outcomes of interest. At this stage, 18 papers were excluded:

- studies on different commercial or experimental systems: 10
- letters to editors: 4
- same study in a different journal: 1
- incorrect setting (not at point of care): 1
- cost-effectiveness studies: 2.

Ten studies remained, which included 1 randomised controlled trial and 9 diagnostic accuracy studies that included a reference standard. Two diagnostic accuracy studies were further excluded because they did not include a suitable reference standard. Six diagnostic accuracy studies were summarised briefly but excluded from the full evidence review because they did not include primary evidence investigating the feasibility of implementing intrapartum antibiotics based on the results of the intrapartum Xpert GBS test. The randomised controlled trial and the diagnostic accuracy study that assessed the feasibility of intrapartum antibiotic prophylaxis based on Xpert GBS results became the focus of the evidence review.

About this briefing

Medtech innovation briefings summarise the published evidence and information available

for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths and weaknesses of the relevant evidence, but contain no recommendations and **are not formal NICE guidance**.

Development of this briefing

This briefing was developed for NICE by Newcastle and York External Assessment Centre. The [interim process & methods integrated process statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality assured and approved for publication.

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