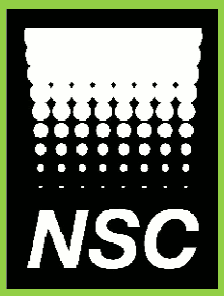


UK National Screening Committee

Screening for Group B Streptococcal infection in pregnancy

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

Version: 3

Bazian Ltd

July 2012

The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

Template v1.2, June 2010

Contents

Introduction

Group B Streptococcus (GBS, *Streptococcus agalactiae)*, is a Gram positive pyogenic streptococcal bacterium. It is found primarily in the gastrointestinal tract and usually causes no harm to the carrier. GBS can cause invasive disease, mainly in infants, but also in pregnant women, women who have recently given birth, and older adults.

GBS bacteria can colonise the vagina and in pregnant women can be passed on to the baby. This is thought to occur mainly during labour. Not all babies born to GBS colonised women will be colonised, and not all that are colonised will go on to develop invasive GBS disease.

Invasive GBS disease in newborns before 7 days of age is generally referred to as early onset GBS (EOGBS), although this term is sometimes used to refer to GBS disease occurring in the first 48 hours of life. EOGBS is usually thought to be due to mother to baby (vertical) GBS transmission. GBS disease occurring from 7 days up to three months of age are referred to as late onset GBS (LOGBS).

Infection in babies with GBS can be superficial, such as skin infections; deep localised infections such as pneumonia; or systemic infections such as septicaemia or meningitis. GBS infection can be fatal, with mortality rates higher in preterm babies.

Antenatal screening for maternal GBS colonisation

The aim of antenatal screening is to identify GBS colonised mothers for treatment with intrapartum antibiotic prophylaxis (IAP). IAP aims to reduce the risk of EOGBS and death in the newborn. Treatment of GBS colonised women with antibiotics antenatally (before labour) is not effective in preventing EOGBS.[1]

The main strategies used in identifying women eligible for IAP for GBS prevention are:

- A universal screening strategy: This involves testing mothers for GBS, usually using swabs of the vagina and rectum, and then offering IAP to women if they are identified as GBS carriers. Due to the time taken to culture GBS using standard methods, screening is generally done at 35 and 37 weeks of gestation rather than during labour to allow sufficient IAP to be delivered.
- A risk-based approach: This involves identification of women with risk-factors for having a baby with EOGBS such as preterm labour, prolonged rupture membranes or fever during labour, and then offering IAP to these women.

In practice, different aspects of these strategies can be combined. For example, in the US, the CDC currently recommends universal screening at 35 to 37 weeks of pregnancy, with some risk-factor based exceptions (e.g. women known to have GBS bacteriuria in the current pregnancy or who had a previous infant with invasive GBS are offered IAP without the need for screening).[1] For women who present before a swab has been taken or before the results are ready, the CDC guideline recommends using a risk factor based strategy to decide whether women should receive IAP.

Current policy

Current policy is that antenatal GBS screening in pregnancy is not recommended by the National Screening Committee. The last review of this policy took place in 2008/2009 and concluded that this policy should not be changed.[2]

In 2003 the Royal College of Obstetricians and Gynaecologists recommended a risk-based approach for identifying women who may benefit from IAP for early onset GBS prevention.[3]

This report

Update reports aim to assess whether the evidence base has changed sufficiently since the last NSC policy review to warrant consideration of changing the policy. Update reports provide an overview of key evidence published since the previous policy review. They are not systematic reviews and do not reassess the evidence underlying the previous policy decision.

The previous NSC policy review in 2008 decided not to recommend screening for GBS in pregnancy. This update report assesses the evidence relevant to universal screening for GBS in pregnancy published from 2008 to February 2012.

The report structures the discussion of this evidence using the UK National Screening Committee (NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme (National Screening Committee 2003). Update searches were performed to identify the international literature relating to GBS screening in pregnancy between 2008 and February 2012. Additional references were provided by the GBS Support group (see Methodology section for details).

This update report focuses on post-2008 evidence that is relevant to antenatal screening of pregnant women for GBS carriage in the UK, as this is the policy under review.

We have referred to the most recent NSC update report from 2008[2] where appropriate, to provide background to the new evidence identified. The main barriers to screening identified in the 2008 report included:

- Lack of RCT evidence assessing the effects of the screening strategies
- The low incidence of EOGBS neonatal sepsis in the UK without screening
- Uncertainties about the effectiveness of intrapartum antibiotic prophylaxis in preventing EOGBS sepsis (culture proven and probable)
- Concern about the safety of intrapartum antibiotic prophylaxis

This report therefore concentrates on these areas, and other areas where new evidence was identified, such as the performance of the test.

Systematic searches of the international literature published between January 2008 and October 2011. This search yielded 1,035 publications (after removal of duplicates), of which 302 were selected as being potentially relevant (see Methodology section for study breakdown). The charity Group B Strep Support (GBSS) provided a list of about 90 references published since 2008. Some of these studies were published after the original search date (October 2011), so a top-up search using the original search strategy was carried out to identify studies published between October 2011 and February 2012. This search yielded 156 publications (after removal of duplicates), of which 46 were selected as being potentially relevant (see Methodology section for study breakdown). These references overlapped with those provided by GBSS. Other relevant references identified during the preparation of this report have also been included.

A first pass appraisal at abstract level was followed by a retrieval of selected full text papers. Guidelines, systematic reviews, and RCTs, as well as studies from the UK were prioritised, as were studies addressing key areas of uncertainty identified in the previous update report. An overview of the most informative and relevant references regarding the individual screening

criteria is given in this report. Further information on how studies were selected is reported in the Methodology section at the end of this report.

Based on the evidence reviewed we have made provisional summary statements about whether each criterion is met, not met, partially met, not clear if met, or is not applicable. These judgements are provisional and should be reviewed by the UK NSC in the context of all the evidence available.

Summary

The evidence reviewed did not identify any information that changes the view of EOGBS disease as an important health problem. The incidence of EOGBS in the UK appears to have remained broadly in line with the incidence described in the British Paediatric Surveillance Unit study published in 2004, which calculated an incidence of 0.48 per 1,000 livebirths (95% CI 0.43 to 0.53 per 1,000 livebirths) in the year 2000-2001. Figures from the Health Protection Agency suggest a small increase in EOGBS bacteraemia between 2003 and 2010 in England, Wales and Northern Ireland as a whole, from 0.37 per 1,000 livebirths to 0.41 per 1,000 livebirths. Whether this change is statistically significant has not been tested, and whether it reflects changes in voluntary reporting of cases, natural fluctuation, a true increase in incidence, less than optimal implementation of prevention strategies, or other reasons is uncertain. These figures come from voluntary reporting of culture-proven GBS bacteraemia, and therefore may not represent all cases of GBS bacteraemia. The figures also apply to livebirths, therefore do not include stillbirths where GBS is present.

EOGBS remains the most common cause of early onset neonatal sepsis in England. Estimates suggest that the death rate among infants with EOGBS in the UK remains around 10% overall. About 31 babies may die from EOGBS each year in the UK (excluding Scotland). This figure does not include stillbirths relating to GBS.

One UK case control study supported an association of certain risk factors with invasive GBS disease. This included being found to be colonised by GBS in pregnancy (not screening detected, as screening is not offered in the UK), GBS bacteriuria, fever in labour, and prolonged rupture of membranes. Being found to be colonised by GBS and fever in pregnancy remained significantly associated when adjusting for all other factors, with longer duration of ruptured membranes just missing out on significance.

The natural history of GBS carriage in pregnant women is only partly understood, with colonisation status as detected by antenatal culture at 35 to 37 weeks not remaining stable until the time of delivery in some women. The reasons for the changes in colonisation status are not clear. Although a considerable proportion of pregnant women are colonised with GBS, approximately 21% in the UK, very few go on to have babies affected by EOGBS.

Recommendations for UK practice come from a 2003 Royal College of Obstetricians and Gynaecologists guideline, which is currently under review. This encourages the use of antenatal and intrapartum risk factors to guide the use of preventative treatment. One study from the UK suggested that about two thirds of mothers of EOGBS cases have at least one risk factor for EOGBS. This means that a third of EOGBS cases might be born to women with no known risk factors for GBS, and therefore not targeted with IAP in the absence of universal screening. The approach to screening used in countries such as the US incorporates both swab based screening and a risk factor based approach to guide IAP, therefore risk factor based management may not

be replaced entirely by screening if screening were recommended. Rather the two approaches may run concurrently as components of a broad prevention strategy.

There is still no vaccine available for the prevention of GBS colonisation and infection, although early stage research into this possibility is ongoing.

The standard method of identifying GBS colonisation in pregnancy is currently a culture of vaginal-rectal swabs. Due to the time taken to obtain results using this method (around 3 days) and to take account of changes in colonisation status over time, screening for GBS colonisation is usually done between 35 to 37 weeks' gestation in countries that recommend universal screening. The purpose of screening is to select an intrapartum antibiotic treatment group.

The ability of antenatal testing to predict intrapartum colonisation with GBS is moderate. One systematic review found that on average about 70% of women who test positive for GBS on antenatal screening after 35 weeks' gestation also test positive during labour, and on average about 5% of women who test negative on antenatal screening will test positive during labour. The largest recent study looking at the performance of antenatal screening in routine clinical practice in the US found less accuracy in practice (a PPV of 50.5%, and an NPV of 91.7%). If only those women screened at the recommended time (35 to 37 weeks' gestation) were considered the positive predictive value improved to 60.6%, with the NPV remaining similar (89.5%).

Establishing test sensitivity at the point of screening is not currently feasible because of the absence of a gold standard comparator. A recent study looking at EOGBS in the US in 2003-2004 found that the number of affected babies born to women with negative antepartum screening results was higher than they estimated based on the literature; the reasons for this were unclear.

There still appear to be no post-screening methods available for narrowing down which mothers colonised with GBS are at the greatest risk of having an infant affected by EOGBS.

Due to the limitations of antenatal GBS culture screening, there is interest in developing rapid testing methods that can be used intrapartum. Real time PCR appears to be the most promising of these methods. One study of particular interest used a real time PCR system operated in the labour ward by midwives. This type of system is likely to be the most practical way to ensure that rapid testing would be available at all times, and not require specialist operators. Overall, real time PCR shows promise for potential use in the labour ward, but has not been sufficiently studied in this setting to be ready for widespread adoption as yet.

Prevalence, epidemiology, natural history and current clinical guidelines define the population to be tested and the burden of disease on which screening might be expected to impact as part of a wider prevention strategy. Screening at 35-37 weeks would miss a proportion of premature deliveries (generally considered as deliveries before 37 weeks' gestation), case fatality among babies with EOGBS delivered prematurely is higher than among term babies. Also, some women with risk factors are not tested in current screening programmes, and the screening test result does not affect the intrapartum management strategy for others. The population which would be screened, and in whom screening would direct management, would be likely to be mainly term women with no risk factors.

Intrapartum antibiotic prophylaxis (IAP) is the mainstay of prevention of EOGBS. No additional RCTs assessing the effects of IAP on EOGBS have been published since the last NSC update report. A systematic review found that the available RCT evidence suggests that intrapartum antibiotic prophylaxis reduces culture confirmed and probable EOGBS. IAP was not shown by

these RCTs to reduce neonatal mortality from GBS or from all causes. Only one study looked at death as an outcome and it may have lacked power to detect differences. The review noted that the existing RCTs were small, of poor quality, and were performed about 20 years ago. It concluded that giving antibiotics is not supported by conclusive evidence. It also noted that performing new, adequately sized double blind RCTs may not be possible now that practice guidelines recommending the use of intrapartum antibiotics have been introduced in many areas.

Based on the existing evidence and expert consensus, IAP is recommended by US and UK bodies for reducing EOGBS risk in pregnancies identified as being at risk via screening or risk based approaches.

There have been no RCTs assessing the effects of antenatal screening for reducing deaths or morbidity from EOGBS. In the absence of RCTs it is difficult to quantify the potential impact of adding antenatal screening for GBS to current clinical practice. The literature identified did not report on the long term impact on the offspring of expanding intrapartum antibiotic use. A proportion of women who screen positive for GBS carriage antenatally will no longer be carriers at the point of treatment, and this introduces an additional level of uncertainty.

Several countries have implemented universal antenatal screening including the US. The US has seen a considerable decrease in the incidence of EOGBS from about 1.7 livebirths per 1,000 to less than 0.5 per 1,000 livebirths since guidelines on IAP were introduced in the 1990s. Initially recommendations suggested that IAP could be guided by either antenatal bacteriological screening or a risk based strategy. Universal screening was recommended in 2002 in the US. After this there was a period of increase in EOGBS between 2003 and 2006, but this does not appear to be continuing. Provisional figures for 2010 suggest that the incidence was 0.26 per 1,000 livebirths, but these figures have not been finalised as yet and therefore may change.

Changes seen in before and after studies such as this are difficult to conclusively attribute to the introduction of screening, as other changes over this period may also have had an effect. There is also the suggestion that the changes may reflect a decreased likelihood of cultures being positive due to increased IAP use, with the culture negative cases of EOGBS sepsis being undetected in these surveillance figures. One study from the US suggested that this may not be the case, based on the observation that the proportion of neonatal sepsis cases in the three months after birth where a pathogen was identified had not changed between 1988 and 2006.

No new cost-effectiveness studies on GBS screening in the UK have been carried out since the last update report in 2008. A recent study of the financial cost of GBS in the first two years of life suggests that the additional cost of healthcare resources required to care for EOGBS babies is about £3,000 higher than for babies without EOGBS. This additional cost was mainly for preterm babies with EOGBS, with little difference in costs between term babies with and without EOGBS.

It remains difficult to weigh up the benefits and harms of antenatal GBS screening. EOGBS in the UK is relatively uncommon, occurring in about 0.5 per 1,000 livebirths in the UK, and deaths from EOGBS may be about 0.05 per 1,000 livebirths. As about 21% of women in the UK are estimated to be colonised by GBS antenatally, intrapartum antibiotics would be required in about 210 women per 1,000 pregnancies. A crude comparison based on figures from a UK HTA suggests that a similar proportion of women have at least one risk factor for EOGBS. The harms in terms of anaphylaxis are likely to be rare, but are serious. In addition, the potential for increasing antibiotic resistance is a harm on the population level, and this is difficult to balance against potential individual-level benefits.

Appraisal against UK NSC Criteria

These criteria are available online at http://www.screening.nhs.uk/criteria.

1. The condition should be an important health problem

2008 Update report: *"Maternal carriage of GBS can result in transmission of the organism to the fetus which can then result in stillbirth or neonatal sepsis, and it can result in post-partum infectious morbidity in the mother."*

"Although [early onset GBS] EOGBS neonatal sepsis is uncommon, occurring in 0.5 per 1000 livebirths, it is an important health problem with a case fatality in preterm babies (less than 37 weeks gestation) of 18% and a case fatality in term babies of 8%. In survivors of EOGBS neonatal sepsis there is an increased risk of neurological problems including cerebral palsy, deafness, blindness and profound cognitive impairment."

EOGBS incidence

The EOGBS figures quoted in the 2008 update report[2] came from a British Paediatric Surveillance Unit (BPSU) study covering the period February 2000 to February 2001 in the UK and Ireland, published in 2004.[4]

Below we discuss information published relating to EOGBS in the UK since 2008.This includes a recent systematic review of global literature,[5] as well as data from the UK Health Protection Agency.[6]

A recent systematic review described the global burden of culture-confirmed GBS disease in infants aged under three months (i.e. both early onset and late onset GBS disease) in studies published since 2000.[5] It found that the average global incidence of EOGBS was 0.43 per 1,000 livebirths (95% CI 0.37 to 0.49) and the average case fatality rate was 12.1% (95% CI 6.2% to 18.3%). It did not provide pooled EOGBS incidence by country, but did report that the mean incidence was highest in Africa, followed by the Americas, Europe, and then southeast Asia (see Table 1). The only factor significantly associated with EOGBS incidence was use of intrapartum antibiotic prophylaxis (IAP). The rate of EOGBS in studies that reported no use of IAP was significantly higher than in studies that reported any use of IAP (incidence per 1,000 livebirths: 0.75 with no IAP vs. 0.23 with any IAP; OR 2.20, 95% CI 1.59 to 3.40). Most of the European and American studies reported use of IAP, while most studies from Africa and the Eastern Mediterranean reported no IAP use. Other differences between countries may contribute to the differences seen. The other factors assessed were not significantly associated with EOGBS rate (World Health Organization region, gross national income, skilled attendance at delivery, prospective or retrospective study design, delivery site, reporting period, specimen type used to confirm GBS disease, or low birthweight). The association between GBS screening and EOGBS rate was not investigated by the review.

Table 1: Global rates of EOGBS per 1,000 livebirths

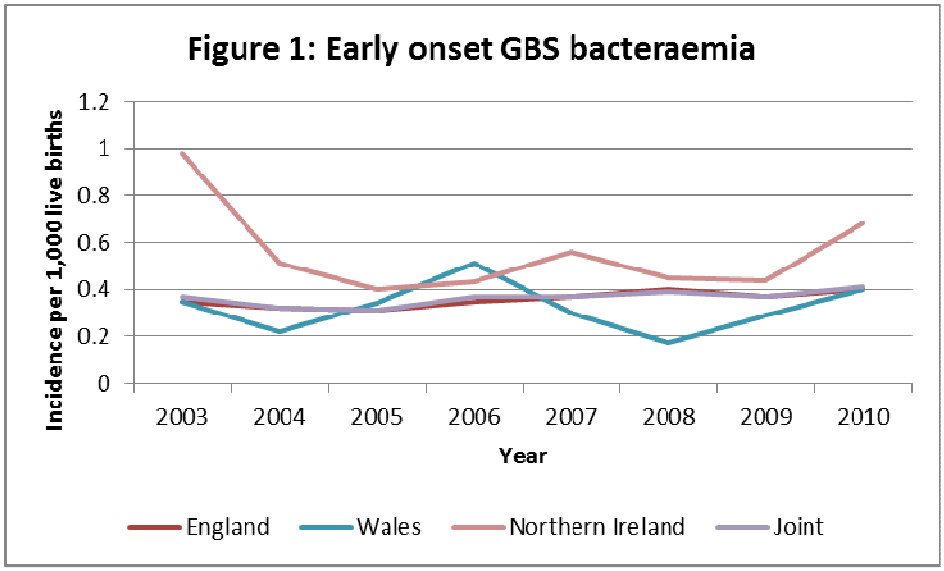
Area	Rate of EOGBS per 1,000 livebirths (95% CI)
Africa	0.53 (0.15 to 0.92)
The Americas	0.50 (0.43 to 0.57)

Europe	0.45 (0.34 to 0.56)
Southeast Asia	0.11 (0.012 to 0.220)

Four of the papers identified by this systematic review assessed GBS incidence in the UK (Heath et al 2004 covering 794,037 livebirths; Oddie et al 2002 covering 62,786 livebirths; Weisner et al 2004 covering 654,474 livebirths; and Vergnano et al 2011 covering 130,763 livebirths). The 2011 study was performed by the neonatal infection (neonIN) surveillance network and is described along with other studies relating to on EOGBS incidence in the UK in Criterion 2.[7]

Data from the Health Protection Agency (HPA) was assessed to determine the reported incidence of EOGBS bacteraemia in the UK.[6] This data comes from voluntary submissions from laboratories in England, Wales, and Northern Ireland and does not include clinical data, so the clinical characteristics of these GBS bacteraemia cases cannot be determined. The figures will not include cases where GBS bacteria are not detected in sterile site testing, or stillbirths.

The HPA figures for early onset GBS bacteraemia are shown in Figure 1 below.



The Health Protection Agency (HPA) received 302 reports of babies with EOGBS bacteraemia in England, Wales, and Northern Ireland in 2010, giving an incidence of 0.41 per 1,000 livebirths (see Criterion 2 below for more detail on EOGBS incidence in the UK). According to HPA data, the rate of early onset GBS (EOGBS) bacteraemia in England, Wales and Northern Ireland increased slightly from 0.37 per 1,000 livebirths in 2003 and 0.41 per 1,000 livebirths in 2010. The difference in incidence equates to one additional case of EOGBS bacteraemia per 25,000 livebirths. Whether this trend is statistically significant has not been assessed, therefore it is not possible to say whether it is outside of what would be expected due to chance fluctuations. In all years in this period the overall reported incidence remained below 0.5 per 1,000 livebirths.

Over this period figures for England closely mirror the joint figures, as England contributes the largest population; the figures for Wales and Northern Ireland have varied more widely. In general, the figures for Wales have mostly been the same or lower than those for England, and

those for Northern Ireland have been higher. In Northern Ireland there were reported to be 0.98 cases of EOGBS per 1,000 livebirths in 2003 and 0.68 per 1,000 livebirths in 2010.

The rate of late onset GBS (LOGBS) has also shown a trend for increase. The reported rate in England, Wales, and Northern Ireland was 0.18 per 1,000 livebirths in 2003, and 0.28 per 1,000 livebirths in 2010. The joint figures for LOGBS have remained under 0.3 per 1,000 livebirths over this period. The figures for England again closely mirror the joint figures for the three countries, while the figures for Wales and Northern Ireland have varied more widely.

These figures are based on voluntary surveillance data, and may not represent all cases of EOGBS bacteraemia in these countries. The completeness of reporting may also vary across regions or different years. This makes drawing firm conclusions based on these figures difficult. As a general indicator of the completeness of voluntary surveillance reporting the HPA has looked at how voluntary reporting of a different pathogen, *Staphylococcus aureus*, compares to mandatory reporting of this pathogen in England.[8] Levels of voluntary reporting of *S. aureus* were 75% of the levels of mandatory reporting in 2003 and 76% in 2004, increasing to 82% in 2008; since then it has remained at around this level.(HPA , personal communication and [8]) By analogy, these figures may give an indication of the completeness of voluntary reporting of GBS bacteraemia. If an increasing proportion of cases have been reported over time this would lead to an apparent increase in incidence, even if incidence has remained stable. As there is no mandatory reporting of GBS infections it is not possible to verify that the trend in voluntary reporting of GBS has been the same as that for *S. aureus*.

EOGBS case fatality rate in the UK

The update search identified one study assessing the case fatality rate of EOGBS in the UK and one for the Republic of Ireland, the latter is included due to its proximity to Northern Ireland.[9,10] It also identified one study that reported the case fatality rate for invasive GBS (early and late onset) in England.[11]

An analysis by the HPA linking their data to Hospital Episode Statistics and Office for National Statistics death registration data suggested that the case fatality rate of EOGBS in England in 2009 was 5%.[12] In addition, 4 out of 101 (4%) cases of invasive GBS infection in pregnant women where the outcome was known resulted in stillbirth.

The first UK study analysed data collected by the neonIN surveillance network between 2004 and 2007.[9] The neonIN network collects data on the pathogens causing neonatal disease and their antibiotic sensitivity, and matches this with clinical data. It started collecting data from four neonatal units in 2004, and this increased to nine by 2007.[7] It found that among the 48 cases of EOGBS in this period there were five deaths (10.4%), but that only three of these (6%) were attributable to invasive GBS disease.[9] The causes of the two deaths not attributed to invasive GBS disease were not reported. The total death rate in this study (10.4%) is the same as the overall rate reported for the UK in 2001 (39 deaths among 376 cases of EOGBS) as quoted the 2008 update report for the NSC.[2]

The second UK study looked at the case fatality rate for early and late onset GBS cases in four areas in England (Greater London, Oxford, Portsmouth, and Bristol) between 2000 and 2003.[11] Of the 138 cases of GBS disease, 74% were of EOGBS. The overall case fatality rate in this study was 9.4%.

The study from the Republic of Ireland reported that the case fatality rate for EOGBS in one hospital in between 2004 and 2009 was 11%.[10] This estimate was based on a small number of

EOGBS cases (9 cases and 1 death), so may not be a reliable indication of national rates. If these figures are pooled with cases from an earlier period (1996 to 2002) in the same hospital quoted in the study, the overall case fatality rate was 4.2% (1 death in 24 cases).

GBS as a cause of early onset sepsis in the UK

2008 update report: *"GBS is recognised as the most frequent cause of early onset neonatal sepsis."*

The update search identified one study assessing the causes of early onset sepsis in the UK. [7] This study confirmed that GBS was the most common cause of early onset sepsis in England (defined in this study as sepsis in the first 48 hours of life).[7] It reported data on the incidence of neonatal sepsis collected by the neonatal infection (neonIN)[6] surveillance network in England between 2006 and 2008. Sepsis was defined as positive culture from a normally sterile site (blood, cerebrospinal fluid, or suprapubic aspirate) for which antibiotics were prescribed for at least five days. Data was collected from eight units in 2006, nine in 2007, and 12 in 2008. It found that GBS was responsible for 52% of the cases of early onset sepsis (65/125 cases).

This was equivalent to about 0.5 cases of GBS early onset sepsis per 1,000 livebirths. Changing the definition of early onset sepsis to sepsis occurring before 7 days of age only added three new cases of early onset GBS sepsis, taking the total number from 65 to 68 (in 130,763 livebirths). This made a small change to the incidence of early onset GBS sepsis (from 0.497 to 0.520 per 1,000 livebirths). The rate of early onset GBS sepsis did not change significantly between 2006 and 2008 (p value not reported).

GBS was not the most common cause of late onset sepsis (sepsis after 48 hours), being responsible for only 8% of cases, which was equivalent to 0.3 cases of late onset GBS sepsis per 1,000 livebirths).

GBS and neonatal death in the UK

One study from England and Wales was identified which described the contribution of infections to neonatal deaths (before 28 days of age) using death certificate data from 2003 to 2005.[13] The study did not distinguish between cases of early and late onset GBS disease. It found that infections accounted for 0.4 neonatal deaths per 1,000 livebirths, which equated to 11% of all neonatal deaths in this period. GBS was reported in 32% of cases where bacterial infection was specified (87/273 cases), this equated to 11% of all infection-related neonatal deaths (87/768 cases), and 1.3% of all neonatal deaths (87/6,700 cases). This suggests that GBS may be a recorded pathogen in about 0.045 neonatal deaths per 1,000 livebirths.

This figure is broadly in line with what might be expected if the rate of EOGBS disease in the UK is 0.41 per 1,000 livebirths and the case fatality rate is in the region of 10%, which would give an expected EOGBS-related death rate of 0.041 per 1,000 livebirths. A 10% case fatality rate would suggest that about 31 deaths from EOGBS may occur in England, Wales and Northern Ireland annually (10% of the 302 cases of EOGBS bacteraemia reported to the HPA in 2010).

A higher proportion of neonatal deaths where a bacterial infection was reported were attributed to GBS among term neonates with no comorbidities than among preterm neonates (58/111 [52%] in term no comorbidities vs. 29/162 [18%] in preterm; $p<0.0001$).

The study authors note that death certificate data has known limitations, including that the information on the certificates is limited and may be incomplete. For example, the age at onset

of the infection is not recorded meaning that it was not possible to determine which cases would be classed as early onset, and which late onset. In addition, information on specific pathogens and comorbidities may not be complete. They say that linking of microbiological, prescribing and clinical outcome data is needed to identify how best infection related deaths can be reduced.

Effects of GBS carriage on premature labour

The update search identified one systematic review looking at the impact of maternal GBS colonisation on risk of preterm delivery.[14] Twenty studies (45,888 women) met inclusion criteria: 11 cohort studies, five cross sectional studies, and four case control studies. The studies varied in country, timing of GBS testing, sites swabbed for GBS colonisation, culture methods used to detect GBS, and exact outcome assessed (preterm labour or preterm delivery). These variations may reduce the reliability of the pooled results. Few studies (only three out of 20) adjusted for potential confounding factors.

The cohort studies found no association between GBS colonisation during pregnancy and subsequent preterm labour/delivery (RR 1.06, 95% CI 0.95 to 1.19). There was significant heterogeneity in this analysis (p=0.02). The cross sectional studies found that preterm labour/delivery was more common among those with GBS colonisation at the time (RR 1.75, 95% CI 1.43 to 2.14). There was again significant heterogeneity in the results (p<0.00001).The case control studies found that GBS colonisation was more common in women having preterm labour/delivery than in those at a similar gestational stage who were not having preterm labour/delivery (OR 1.59, 95% CI 1.03 to 2.44; p for heterogeneity = 0.74). For the case control and cross sectional studies, the timing of GBS colonisation relative to the onset of preterm labour is not known; therefore it is difficult to establish whether GBS could have contributed to causing premature birth.

These results should be interpreted with caution due to the heterogeneity of study designs and of the results and the potential for confounding. Overall they suggest that GBS colonisation in pregnancy is not clearly associated with an increased risk of preterm birth.

Summary: Criterion 1 Met

The papers identified in the update search did not identify any information that changed the view of EOGBS disease as an important health problem. One new study suggested that GBS remains the most common cause of early onset neonatal sepsis in England, estimating that it accounts for just over 50% of cases of sepsis that occur in the first 48 hours of life.[7]

According to the most recent data available from the Health Protection Agency the overall incidence of EOGBS bacteraemia in England, Wales, and Northern Ireland in 2010 was 0.41 per 1,000 livebirths. Studies suggest that the case fatality rate among infants with EOGBS in the UK may be between 5% and 10%. Based on these figures there may be about 31 neonatal deaths related to GBS in England, Wales and Northern Ireland annually. This is broadly consistent with the BPSU study published in 2004, which found an overall rate of EOGBS across the UK and the Republic of Ireland the year 2000-2001 of 0.48 per 1,000 livebirths (95% CI 0.43 to 0.53 per 1,000 livebirths), and a case fatality rate of 10.6% (377 cases of EOGBS overall and 38 deaths).[4]

One systematic review suggested that GBS carriage in pregnancy is not clearly associated with an increased risk of preterm birth; the underlying studies had limitations to their methods that may affect the reliability of this conclusion.

2. 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, disease marker, latent period or early symptomatic stage

Epidemiology and natural history of GBS carriage in pregnant women in the UK

2008 update report "*The natural history of EOGBS carriage in the lower genital tract of pregnant women is not well described*. *Swabs taken in early pregnancy are not as predictive of vaginal carriage at the time of birth as swabs taken late in pregnancy. Whether this means that the organism is no longer present in the vagina or merely that levels of the organism are lower at different times is uncertain. And although there is evidence to suggest that the risk of transmission from the lower genital tract to the baby varies depending on the bacterial load in the vagina at the time of birth, transmission can occur when women have negative cultures."*

"Around 21% of mothers in the UK appear to be GBS carriers."

Rate of maternal GBS colonisation in the UK

One systematic review describing the prevalence of maternal GBS colonisation in Europe was identified,[15] as well as two subsequent studies from the UK which described the rate of maternal colonisation with GBS either antenatally or during labour. [16-18]

The systematic review searched for studies published up to 2006 from Europe, and included 21 studies.[15] One of these studies came from the UK (748 women), and two from Ireland (707 women).The UK study was the only one of these three studies which was categorised as being of high quality (Jones et al 2006). It collected combined vaginal/rectal swabs after 34 weeks' gestation and used selective broth medium. It found a maternal colonisation rate of 21.3%.

The first subsequent study was part of a UK HTA report looking at the test characteristics of rapid intrapartum GBS tests. [17,18] This HTA was in press at the time of the 2008 update of NSC screening policy,[2] and was considered as part of that report. Briefly, it reported that maternal intrapartum GBS colonisation rate was 21% based on vaginal and rectal swabs (n=1,418 women swabbed). This was reported to be higher than that found in a meta-analysis of UK studies (14%) performed as part of a previous HTA,[19] although the meta-analysis reportedly included studies that looked at vaginal colonisation only rather than vaginal and rectal colonisation, which is the recommended approach to swabbing.

The second small study identified assessed GBS colonisation in 100 pregnant women at 34-40 weeks gestation in Manchester.[16] It found that 17% of women were colonised by GBS in low vaginal and/or rectal swabs. An additional 2% of women were colonised by GBS in throat swabs, and another 2% of women were reported to be GBS positive by the enrichment culture method but not by direct culture (location of colonisation not reported for these women, i.e. throat or vaginal or rectal). The main method of GBS isolation used in this study appeared to be direct culture of swabs on blood agar and selective agar plates rather than the HPA recommended method of selective broth followed by agar subculture.[20] This may have reduced the sensitivity of detection. The swabs were reported to also be inoculated onto a selective broth but no detail of subsequent steps used to identify GBS was reported. The small size of this study may mean that the results are not representative of the UK as a whole.

Variation between antenatal and intrapartum maternal GBS colonisation

The literature identified in the update search was in agreement with the previous update report in finding that GBS carriage can vary in pregnancy, and that there can be 'discordance' between GBS colonisation status at 35 to 37 weeks antenatally and colonisation status at the time of labour as tested by culture (see Table 2 below; and Criterion 5). One systematic review and three additional studies focused on comparing the results of antenatal and intrapartum culture.[21-24]

The systematic review suggested that proportion of positive antenatal cultures that remained positive by the time of labour improved the nearer to delivery the antenatal culture was carried out (see Criterion 5 for details).[21] It found that in prospective studies where antenatal screening was performed after 35 weeks on average 29.8% of women positive at screening were negative for GBS on intrapartum testing, and 4.8% of women negative at antenatal screening were positive on intrapartum testing.[21]

The results of the review and three additional studies identified in the update search that focused on the performance of antenatal screening are shown in Table 1 below.

The largest additional study (n=4,696 successfully cultured at both time points and analysed) was carried out in the US, and found that among women screened antenatally at 35 to 37 weeks' gestation, 39.4% of women positive for GBS carriage at screening were negative for GBS carriage during labour, while 10.5% of those negative for GBS carriage at screening were positive at labour.[22] Further detail on this study (Lin 2011) is provided in Criterion 5. This study found no significant difference in use of antibiotics in pregnancy between those women whose antenatal tests remained positive at labour (15.2%) and those whose tests were positive antenatally, but negative in labour (18.6%; p=0.29). This suggests that the change seen in colonisation status over time was unlikely to be a result of antibiotic usage, at least in most cases.

The results of these studies may reflect natural variation in colonisation status within the vagina/rectum over time. In some studies they may also reflect the fact that the antenatal and intrapartum tests are being performed by different providers, who may differ in their proficiency in and methods for colonisation detection (see Criterion 5 for further discussion of these studies).

Table 2: Changes in culture detected GBS status between antenatal and intrapartum testing

Study author, year, design and participants	% of women with positive antenatal tests who were negative at labour	% of women with negative antenatal tests who were positive at labour	Comments
Valkenberg 2010[21] Systematic review	29.8% for women screened after 35 weeks	4.8% for women screened after 35 weeks	Figures calculated from the reported average PPV and NPV figures for prospective studies in which screening took place after 35 weeks. Numbers of women included in this analysis not reported.
Lin 2011[22] Primary study	39.4% for women screened at 35 to 37	10.5% for women screened at 35 to 37	Different laboratories performed the AN and

Study author, year, design and participants	% of women with positive antenatal tests who were negative at labour	% of women with negative antenatal tests who were positive at labour	Comments
n=4,696 analysed	weeks	weeks	IP cultures No significant difference in antibiotic usage during between women whose AN and labour cultures were both positive (15.2%), and those whose who were positive AN but not at labour (18.6%; p=0.29)
Towers 2010[24] Primary study n=1,472 analysed	33.0% for late third trimester screening	11.6% for late third trimester screening	Different laboratories performed the AN and IP cultures Women who used antibiotics in the 14 days before labour were excluded, but other antibiotic use in pregnancy was not discussed
Kovavisarach 2008[23] Primary study n=302 analysed	29.3% for women screened at 35 to 37 weeks	4.6% for women screened at 35 to 37 weeks	Unclear if there was any antibiotic usage between antenatal screening and delivery

Rates of vertical GBS transmission and of resulting EOGBS disease

2008 update report: *"In approximately 21% of women GBS can be isolated from the lower genital tract during pregnancy. In the UK this amounts to approximately 143,000 pregnant women a year. Of these 143,000 women, there were 376 cases of culture proven EOGBS sepsis in 2001. This represents a transmission risk of approximately 0.3%. Of these 376 cases of culture proven EOGBS neonatal sepsis, there were 39 deaths. Therefore for every woman who carries GBS in the lower genital tract in late pregnancy the risk of neonatal death from EOGBS neonatal sepsis is 0.03%, or 3 per 10,000."*

No new studies providing information on the risk of vertical GBS transmission and of resulting EOGBS disease from the UK were identified.

The most recent UK data came from the UK HTA that was considered as part of the previous NSC update report. [18] It found that neonatal colonisation occurred in 36% of neonates (99/273) whose mother was found to have intrapartum GBS colonisation. This was reported to be similar to the transmission rates found in a previous meta-analysis of UK studies (including 308 colonised women) carried out as part of a previous HTA.[19]

When divided by exposure to intrapartum antibiotic prophylaxis (IAP), neonatal GBS colonisation was 36% (5/14) in babies born to GBS-positive mothers zero to two hours after IAP, 25% (5/20) in babies born three to six hours after IAP, and 5% (1/20) in babies born seven or more hours after IAP (p for trend = 0.02). Among babies whose GBS-positive mothers did not receive IAP the neonatal colonisation rate was 40% (88/219; no statistical comparison with this group provided).

In addition, 1% of women who were culture negative on intrapartum testing had neonates colonised by GBS. In these cases it is possible that culture methods failed to detect the presence of GBS, or that GBS may have been acquired by the baby from the environment. The latter explanation seems unlikely given that neonatal swabs were collected as soon as possible after birth from the external ear canal rather than from a site more exposed to the environment.

Three babies in this study were diagnosed with EOGBS disease, all of whom recovered. Two of these were born to women who had fever in labour and were given intrapartum antibiotic prophylaxis. The third baby was born to a woman without risk factors. All three mothers were colonised with GBS intrapartum. Overall this gave a rate of 2.14 per 1,000 livebirths (confidence interval not provided).[18] This is higher than the rate from the BPSU study published in 2004, and the HPA reported rate of EOGBS bacteraemia for the UK, but the researchers noted that their study was small and the figures were not inconsistent with UK national data from the BPSU study.[4] The HTA report of this study noted that the sample was too small to compare EOGBS rates with previous reports.[17]

All of the neonates with EOGBS were born to mothers with GBS colonisation. This suggests a rate of EOGBS disease among offspring of women with GBS colonisation in labour of about 1% (3 EOGBS cases/294 women with intrapartum GBS colonisation). However, the small number of EOGBS cases means that these estimates may not be reliable.

GBS serotypes

There are ten known GBS serotypes classified based on the capsular polysaccharides and protein antigens that they possess: Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX.[25] Two systematic reviews were identified that reported on GBS serotype prevalence.[5,15]

The first systematic review reported on maternal GBS colonisation in Europe.[15] It found that in studies from Eastern and Western Europe and Scandinavia serotype III was the most common (about 30% of 940 isolates tested in six studies), and in Southern Europe serotypes II and Ia were the most common (among 381 isolates tested in three studies). In the study from the UK, serotype III was the most common serotype (26.4%), followed by Ia (25.8%), V (18.9%), Ib (15.7%), II (9.4%) and other serotypes (3.7%).

A systematic review describing the global burden of GBS disease in infants aged under three months also reported on the serotypes of GBS that cause EOGBS and LOGBS.[5] It included 38 relevant studies published between 1980 and 2011. When looking specifically at the serotypes that caused EOGBS, the review found that 37% of EOGBS isolates were serotype III and 40% were serotype I. This was different from LOGBS, where 53% of isolates were serotype III and 30% were serotype I.

Overall almost half of the GBS isolates from infants with GBS disease in these studies were serotype III. This serotype was followed by serotypes Ia, Ib, II, and V in terms of frequency. These five serotypes accounted for more than 85% of GBS isolates in all regions that had serotype data available (including 93% of European isolates). The proportions of the different

serotypes were reported to not change substantially between studies published in the 1980s and 2000s. This data suggest that the profile of serotypes circulating in the UK is similar to elsewhere.

Risk factors for EOGBS

2008 update report: "*There are a number of clinical risk factors which increase the risk of EOGBS sepsis. These include preterm birth (less than 37 weeks gestation), prolonged rupture of the membranes and maternal fever in labour."*

The update search identified one case-control study from the UK quantifying the association between maternal and neonatal factors and early and late invasive GBS in infants.[11]

The study included 138 cases of invasive GBS (57% of the cases at the participating hospitals) and 305 matched controls (25% of those invited to participate; matched to cases for time of birth and birth weight). Most of the cases in this study (74%) were EOGBS; the study did not carry out a separate analysis for early and late onset GBS. The study could not assess whether the participants differed in characteristics from those who declined participation, as they were only allowed to collect information after consent was given from parents. Information on the characteristics of mothers and cases was obtained from their hospital notes.

In unadjusted analysis, mothers of cases were more likely than mothers of controls to:

- Be having their first pregnancy and baby (OR 0.83 per pregnancy, 95% CI 0.70 to 0.98; OR 0.77 per livebirth, 95% CI 0.61 to 0.97)
- Have had GBS bacteriuria in pregnancy (OR 5.55, 95% CI 1.47 to 20.96)
- Be known to have vaginal GBS colonisation (OR 8.47, 95% CI 3.73 to 19.27). The study did not report why some women had been tested for GBS colonisation, or at what point they were swabbed. As the study was from the UK, women would not have universally been offered antenatal GBS screening.
- Had a fever in labour (>38°C OR 5.62, 95% CI 2.03 to 15.55; for every °C increase in maximum intrapartum temperature OR 2.44, 95% CI 1.66 to 3.59)
- Had prolonged ruptured membranes (≥18h vs. <18h OR 2.69, 95% CI 1.67 to 4.34; ≥24h vs. <24h OR 2.37, 95% CI 1.42 to 3.93)
- Have had an epidural in labour (OR 2.15, 95% CI 1.35 to 3.43)
- Have had one or more vaginal examinations during labour (per additional examination OR 1.13, 95% CI 1.03 to 3.62)
- Have had an emergency intervention during delivery such as forceps (OR 2.30, 95% CI 1.42 to 3.62)
- Have an infection after delivery (OR 4.78, 95% CI 1.81 to 12.66)
- Receive post-delivery antibiotics (OR 1.86, 95% CI 1.15 to 3.01).

During labour, cases were also more likely to have fetal tachycardia (OR 2.81), cardiotocographic evidence of fetal distress (OR 2.40), and to need fetal blood sampling (OR 5.33).

There was no difference in use of antibiotics in labour between cases and controls (OR 1.04, 95% CI 0.51 to 2.10; p=0.9).

Factors not associated with GBS disease included young maternal age, black ethnicity, multiple pregnancies, and having had a previous foetal death or baby with GBS disease. The researchers noted that some other studies have found these factors to be associated with GBS disease. They suggested that the reason for this discrepancy may be that these factors are associated with low birth weight, and their study matched infants for birth weight, which would tend to remove any association with these factors.

In multivariate analysis, the factors that remained significantly associated with EOGBS after adjustment were:

- Maternal vaginal GBS colonisation (OR 6.88, 95% CI 2.77 to 17.1; not screen detected, see note under unadjusted analysis results above)
- Maternal infection after delivery (OR 4.17, 95% CI 1.12 to 15.4)
- Having a higher maximum intrapartum temperature (for every °C increase OR 2.16, 95% CI 1.32 to 3.53)

Longer duration of membrane rupture (OR 1.82, 95% CI 0.99 to 3.35; p=0.054) and fetal tachycardia (OR 1.86, 95% CI 0.96 to 3.35; p=0.065) just missed reaching significance.

The UK HTA from 2009 also looked at how many women had risk factors for EOGBS, and the relationship between these risk factors and neonatal colonisation with GBS.[17,18] This HTA was considered as part of the previous NSC update report but is summarised briefly here. It found no association between the presence of maternal risk factors and neonatal colonisation with GBS (unadjusted OR 1.24, 95% CI 0.78 to 1.96; p=0.36; multiple regression also non-significant). However, as there were only a few babies with EOGBS in this study it could not assess the relationship between risk factors and EOGBS disease.

Two uncontrolled studies looked at how prevalent risk factors for EOGBS were among EOGBS cases in the UK and Southern Ireland.[9,10]

The UK study analysed data collected by the neonIN network between 2004 and 2007.[9] Among the 48 cases in this period, median gestational age was 37 weeks, and median birth weight was 2869g. Among the mothers, 67% had at least one risk factor and 44% had two or more risk factors. (Risk factors included were premature rupture of membranes >18 hours, preterm birth at <37 weeks, GBS identified in current pregnancy, fever in labour of >38°C, or a previous infant with GBS).

The study from one hospital in the Republic of Ireland found that between 1996 and 2002, 47% of the mothers of the 15 EOGBS cases had one or more risk factors for EOGBS; two of the mothers (13%) had been swabbed for GBS antenatally and found to be negative.[10] In the same hospital between 2004 and 2009, 33% of mothers of the nine EOGBS cases had one or more risk factors for EOGBS. Four of the six women without risk factors (67%) were found to have vaginal GBS colonisation post-partum. However, it is not possible to say whether these women would have tested positive for GBS colonisation at 35-37 weeks.

Presentation of EOGBS

2008 update report: *"There is no recognised latent period. Women are not aware of vaginal carriage and babies who acquire the infection can become ill very rapidly. Ninety percent of babies with EOGBS sepsis became ill within the first 12 hours after birth, which is not enough time to isolate the organism and provide effective antibiotic therapy before the baby becomes ill."*

The studies identified by the update search also found that EOGBS had a rapid onset in affected babies.[10,11]

The UK case control study on maternal risk factors, described in the previous section, found that the majority of infants with EOGBS presented on the first day of life (89%; 91/102 EOGBS cases).[11] Among these the majority (97.6%) developed clinical features by 12 hours of age (81/83 cases where the hour of onset was noted). Over three quarters of the EOGBS cases in this study presented with sepsis (79.4%), with 11.8% presenting with meningitis, 7.8% with pneumonia, and 1% with focal infections (septic arthritis, osteomyelitis, cellulitis).

Cases had significantly lower Apgar scores at 1, 5 and 10 minutes (OR for each point improvement at 1 min: 0.68, 95% CI 0.58 to 0.80; at 5 min: 0.53, 95% CI 0.40 to 0.71; at 10 min: 0.28, 95% CI 0.11 to 0.72). Cases were also significantly more likely to have respiratory distress or convulsions, and to need oxygen, continuous positive airways pressure, assisted ventilation, surfactant, or tube feeding ($p<0.001$ for all). Cases spent a median of 10 days in hospital (range 1 to 71), compared to 3 for controls (range 1 to 120; $p=0.004$). Longer term morbidity in cases and controls was not reported.

A study from a hospital in the Republic of Ireland found that between 1996 and 2002, 83% of the 15 babies with EOGBS presented within 24 hours of birth, and between 2004 and 2009, two thirds of the nine infants (67%) with EOGBS presented in the first 24 hours after birth.[10] All of the babies with EOGBS born between 1996 and 2002 survived. In the latter period the most common presenting symptom was respiratory distress. All of the affected babies had bacteraemia, and one developed meningitis and marked developmental delay. One infant died from sepsis.

Summary: Criterion 2 Partly Met

The natural history of GBS carriage in pregnant women remains only partly understood. It is known that GBS colonisation status as detected by antenatal culture at 35 to 37 weeks does not remain stable until the time of delivery in all women. Recent studies have reported that between about 30% and 40% of women found to be positive for GBS colonisation antenatally at 35 to 37 weeks' gestation are found to be negative for GBS colonisation at the time of labour. These women may be treated unnecessarily with intrapartum antibiotic prophylaxis (IAP). In addition between about 5% and 12% of women found not to carry GBS antenatally at 35 to 37 weeks' gestation are found to be positive by the time of labour. These women may miss out on IAP that could reduce risk of transmission of GBS.

One study found that about 1% of women who are GBS culture negative during labour have infants colonised by GBS, the reasons for this is unclear, but one possible explanation is that some cases of maternal GBS colonisation are missed by existing culture methods.

One case control study supported an association between maternal risk factors such as GBS bacteriuria, fever in labour, prolonged rupture of membranes and being found to be colonised by GBS in pregnancy and EOGBS in the neonate. Only being known to be colonised by GBS and fever in pregnancy remained significantly associated when adjusting for all other factors, with longer duration of ruptured membranes just missing out on significance. As universal GBS screening is not offered in the UK, GBS colonisation status was not available for all women. The study did not report why some women had been assessed for GBS colonisation.

A UK HTA considered as part of the previous NSC update report found no association between maternal risk factors and neonatal GBS colonisation, but was too small to assess the association

between these risk factors and EOGBS disease. One study from the UK suggested that about two thirds of mothers of EOGBS cases have at least one risk factor. This means that a third of EOGBS cases might be born to women with no known risk factors for GBS, and therefore not targeted with IAP in a risk based approach. Without corresponding figures for all mothers delivering in this period this study cannot tell us what proportion of women who do not go on to have babies with EOGBS have risk factors for EOGBS.

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable

2008 update report: *"No primary prevention is yet possible." …. "There are no currently available vaccines against GBS for use during pregnancy."*

The literature reports that a number of factors have led to interest in developing a GBS vaccine. These include that even in countries where a universal screening strategy has been implemented there are still cases of EOGBS;[26] the practical challenges of delivering adequate IAP to a high proportion of women in labour;[27] screening and IAP do not prevent LOGBS; [28] and the threat of emerging antibiotic resistance.[27,28] Previous cost-effectiveness analyses are reported to have predicted that vaccination could be the most cost effective strategy for prevention if available.[28] However, no vaccine is as yet available against GBS infection.

GBS can be grouped into ten different serotypes, and the prevalence of the different serotypes varies in different countries (see Criterion 2 for further detail).[5,15,25] To be effective, a vaccine would be likely to need to target at least a subgroup of these serotypes. Depending on which subgroups are targeted, the vaccine may have varying efficacy based on the most common serotypes in individual regions. The Europe-wide DEVANI (DEsign of a VAccine against Neonatal Infections) program aimed to better understand GBS epidemiology in Europe to aid vaccine design.[25] A systematic review of GBS disease in infants suggested that five serotypes (Ia, Ib, II, III and V) accounted for more than 85% of the serotypes in all regions of the world where serotype data was available.[5] Therefore they suggest that a vaccine targeting these five serotypes could prevent the bulk of GBS disease in infants globally.

The studies identified by the update search relating to vaccine development all related to animal or laboratory research. A number of early phase RCTs (phases I and II) investigating GBS vaccines in development were identified as ongoing via the Clinicaltrials.gov trial repository, including:

- A phase II RCT looking at the immunogenicity of a trivalent GBS vaccine in healthy pregnant women aged 18-40 years of age is recruiting in Belgium and Canada, with estimated study completion in January 2013 (ClinicalTrials.gov identifier: NCT01446289; sponsored by Novartis)
- A phase II RCT looking at the immunogenicity of a GBS vaccine in HIV positive and HIV negative women in South Africa and Malawi, with estimated study completion in May 2012 (NCT01412801; sponsored by Novartis)
- A phase I/II RCT looking at the immunogenicity and safety of a trivalent GBS vaccine in healthy pregnant and non-pregnant women aged 18-40 years of age in South Africa is ongoing, with estimated study completion in December 2012 (NCT01193920; sponsored by Novartis)

In addition a phase II RCT looking at whether a GBS serotype III vaccine could delay acquisition of vaginal GBS in healthy non-pregnant women aged 18-40 years is reported as having been completed on the Clinicaltrials.gov website (NCT00128219; sponsored by the National Institute of Allergy and Infectious Diseases). According to results shown on the Clinicaltrials.gov website the vaccine did appear to delay acquisition of vaginal GBS colonisation, but its efficacy was reported to be low (p=0.044; vaccine efficacy 36%, 95% CI 1% to 58%).

No phase III RCTs of GBS vaccines were identified as ongoing.

Summary: Criterion 3 Not applicable

There is still no vaccine available for the prevention of GBS colonisation and infection, although early stage research into this possibility is ongoing.

4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

Criterion 4 Not Applicable

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

Recommended methods for detecting GBS colonisation in pregnancy

The UK HPA's National Standard Methods guideline on the processing of swabs for GBS carriage was issued in 2006 and is currently under review.[29] It currently states that the standard method for detecting GBS bacterial colonisation in pregnancy is by culturing either a combined vaginal/rectal swab or two separate vaginal and rectal swabs. It recommends that the swabs should be transported and processed as soon as possible, with delays of over 48 hours undesirable. Transportation in Amies transport medium with charcoal is recommended, and refrigeration is preferable to storage at ambient temperature.

The updated 2010 recommendations from the CDC clarified transport options and timing until processing. They recommend transport of the swabs in non-nutritive transport medium (such as Stuart's or Amies with or without charcoal).[1] They also highlight the fact that recovery of GBS from swabs declines over one to four days, especially at elevated temperatures. Therefore delayed processing and non-refrigeration can lead to false negative results, and the CDC suggests refrigeration before processing.

The HPA recommends that swabs are cultured in selective media (LIM broth) for 18-24 hours, followed by subculture on blood agar for up to 40-48 hours, with first inspection for colonies at 18-24 hours.[29] The CDC's recommendations are similar, but suggest that pigmented media that detect beta-haemolytic bacteria such as GBS can be used, which may avoid the need for subculture onto agar if positive.[1] Direct plating of the swabs onto blood agar plate with or without colistin and nalidixic acid or commercially available chromogenic agar for 18-24 hours is outlined as an option that can be carried out in parallel with enriched selective broth culture. If colonies grow on the agar and are confirmed as GBS then the CDC suggest that the selective broth can be discarded, thus shortening the time taken to obtain results. If plating is negative, then the normal process (using the selective broth and subculture) continues as usual.

The CDC also suggest that rapid tests such as DNA probes, latex agglutination, or nucleic acid amplification tests (e.g. PCR) on enriched selective broth can be used instead of subculture. It recommends the use of enriched selective media for these rapid tests to increase test sensitivity even though this extends the time taken to obtain a result.

Vaginal/rectal GBS colonisation status can change over time, and there has been interest in the possibility of assessing GBS colonisation status during labour. However, due to the time taken to obtain the results of culture tests (testing takes up to about 3 days, not including swab transport time), screening for GBS is performed antenatally rather than during labour, to increase the chances of having sufficient time to provide intrapartum prophylaxis (four hours or longer is recommended by the CDC as an optimal duration). In countries where screening is carried out, it is generally recommended to be carried out at 35-37 weeks' gestation to take into account these practical issues and optimise the ability of the test to predict intrapartum colonisation.

Antenatal culture-based screening

Culture based methods may not detect all cases as GBS colonisation, for example, if low levels of GBS bacteria are present or if there is technical failure in performing swabbing or culture. This possibility is supported by the fact that one study found GBS colonisation in 1% of neonates born to women who have tested negative for GBS colonisation during labour.[18] However, there is no other definitive method to compare it against. Therefore the true sensitivity, specificity, false negative and false positive rates of screening are difficult to gauge.

A second, and perhaps more important, aspect of screening performance is the ability of screening results at 35 to 37 weeks to predict GBS carriage at the time of labour. Screening at 35 to 37 weeks is used to determine who receives IAP. Therefore women identified as being colonised at 35 to 37 weeks by screening but who are GBS negative by the time of labour may receive IAP unnecessarily, and women who screen negative for GBS colonisation at 35 to 37 weeks but are GBS positive by the time of labour may miss out on IAP.

Studies have assessed the ability of antepartum GBS culture-based screening to predict intrapartum culture-based GBS colonisation and this aspect of test performance is focused on in this report. As the same test is being carried out at two different times when colonisation status may not be the same, this is not strictly a diagnostic accuracy study, where a test is compared against an existing gold standard, usually performed at the same time.

Despite this the terms used to report the findings of this type of study are usually those of diagnostic accuracy i.e. sensitivity, specificity, positive and negative predictive value. These terms have also been used here as shorthand to convey how these figures have been calculated. Below we summarise what the terms sensitivity, specificity, positive and negative predictive value refer to when they are applied to studies comparing culture-based screening test at 35 to 37 weeks versus culture-based intrapartum testing in the literature and this update report. In this context:

- Sensitivity refers to the ability of the culture based screening test at 35 to 37 weeks to identify women who will be colonised with GBS at the time of labour based on culture based testing
- False negatives refer to women who screen negative for GBS carriage at 35 to 37 weeks but who are positive for GBS at the time of labour, as determined by culture based testing

- The positive predictive value (PPV) refers to the proportion of positive GBS screening tests at 35 to 37 weeks that remain positive at the time of labour
- Specificity refers to the ability of the culture-based screening test at 35 to 37 weeks to identify women who will not be colonised with GBS at the time of labour based on culture based testing
- False positives refer to women who screen positive for GBS carriage at 35 to 37 weeks but who are negative for GBS at the time of labour, as determined by culture based testing
- The negative predictive value (NPV) refers to the proportion of negative GBS screening tests at 35 to 37 weeks that remain negative at the time of labour

The update search identified one systematic review (search date 2009)[21] assessing the best timing of antenatal tests for GBS, and three additional studies assessing the accuracy of antenatal testing compared with intrapartum culture-based testing.[22-24]

The systematic review included studies which used intrapartum GBS culture as the reference standard, and where the positive and negative predictive values (PPV and NPV) could be calculated. Nine studies met inclusion criteria, seven prospective and two retrospective. These studies included 8,898 women who had both antenatal and intrapartum GBS culture. The studies varied in the swabs taken, with two taking vaginal swabs only, five taking vaginal and rectal swabs (one using peri-anal swabs), one using urine, urethra and rectal swabs, and one using vaginal, endocervical and vaginal wash. Seven out of the nine studies used selective broth media for culture. These variations in methods may influence the accuracy of the tests. The studies all had limitations, with validity scores ranging from 4 to 8 (on a 9 point scale with higher scores indicating greater validity).

Average prevalence at the antenatal swab was 18% (range 6% to 29%; mean gestational age in prospective studies 30.6 weeks, range 10 to 40 weeks), and at delivery was 20% (range 8% to 27%). Mean follow up was 83.5%.

When looking at all studies together, regardless of study design (prospective or retrospective), or timing of antenatal screening, the review found that the average PPV was 69% (range 43% to 100%), and the average NPV was 94% (80% to 100%). Sensitivity ranged from 42.8% to 100% and specificity from 49% to 100% (the 100% rates were based on analyses including 66 or fewer women).

In the prospective studies, testing earlier in pregnancy (before 35 weeks) gave a lower mean PPV (58.8%) than testing later in pregnancy (after 35 weeks; mean PPV 70.2%; only included term births). NPVs were less affected (mean NPV: early testing 93.0%, late testing 95.2%). The retrospective studies did not look at gestational age, rather the number of weeks between the first test and delivery. They also found a trend for higher PPV the closer to delivery the test was carried out (mean PPV: early testing 63.5% vs. late testing 93.2%). The NPV was less affected (mean NPV: 90.2% early vs. 97.5% late).

The UK study included in the systematic review (Easmon et al 1985) used anorectal and low vaginal swabs, and selective media. The prevalence of GBS colonisation at 36 weeks was 20.7%, and at delivery was 16.5%. It found that GBS testing performed at 36 weeks had a sensitivity of 84.3%, meaning that 84.3% of women who had colonisation at delivery were positive for colonisation at 36 weeks, while 15.7% of those with colonisation at delivery had been negative at 36 weeks. There was a specificity of 91.9%, meaning that 91.9% of those without colonisation

at delivery had been negative at 36 weeks, and 8.1% of those without colonisation at delivery had been positive at 36 weeks. The PPV was 67.4%, so 67.4% of those with positive tests at 36 weeks were also positive at delivery; the NPV was 96.7%, so 96.7% of those with negative tests at 36 weeks were also negative at delivery. The review authors noted that although screening between 35-37 weeks did increase the PPV of the test compared to earlier screening, this does mean missing many preterm births, in which GBS sepsis is most dangerous. Preterm birth is generally considered as birth occurring before 37 weeks' gestation, and is a risk factor for EOGBS.

Among the additional studies identified one study from Thailand found no significant difference in PPV and NPV based on time between antenatal culture and delivery.[23] However, this study was relatively small and may have lacked power to detect differences.

One US study found that the PPV was highest when cultures were taken 1 week before delivery (69.7% vs. 54.4% at ≥6 weeks before; p=0.03).[22] Based on its results and other assumptions (number of births annually in the US estimated at 4.2 million and the rate of Caesarean sections estimated at 32%), the authors estimated that in the US there would be:

- 772 cases EOGBS in newborns born to women who screen negative for GBS antenatally (0.18/1000 livebirths)
- 310,097 women who are "over-treated" with antibiotics in labour because they were colonised with GBS antenatally but not at the time of labour
- 14 cases EOGBS in newborns of women with elective Caesarean section without labour or rupture of membranes (these women are not recommended to have IAP in the US).

Overall the additional studies identified in the update search (360 to 5,497 women) found accuracy figures within the broad ranges identified in the systematic review (see Table 3 below for details). They had:

- Sensitivities ranging from 51% to 70.7%
- Specificities ranging from 84.8% to 95.4%
- PPVs ranging from 50.5% to 70.7%
- NPVs ranging from 88% to 95.4%.

Some of the inaccuracy seen in the antenatal test may be due to different providers and laboratories administering the antenatal and intrapartum tests, as was the case in the two US studies. However, this situation may be representative of what occurs in routine clinical practice in the US.

Four additional studies (190 to 758 women) mainly assessing the performance of rapid intrapartum tests also looked at the performance of antenatal culture tests.[30-33] These studies found accuracy figures for antenatal culture testing within the broad ranges identified in the systematic review.[21] They found:

- Sensitivities ranging from 60.5% to 84.3%
- Specificities ranging from 93.2% to 99.2%
- PPVs ranging from 79.7% to 96.3%
- NPVs ranging from 87.9% to 95.5%

Antenatal testing was not the main focus of these studies, so reporting of these results may not have been as thorough and reliable as in the other studies. The results of these are also summarised in the section on rapid testing below, and in Table 5.

Table 3: Accuracy of antenatal culture testing for predicting GBS colonisation during labour (intrapartum)

Author and year	Country; number of women	Swabs	Prevalence	Sensitivity for carriage in labour	Specificity for carriage in labour	PPV for carriage in labour	NPV for carriage in labour	Comments
Valkenberg 2010[21] Systematic review	USA, UK, Sweden, Netherlands, Japan n=8,898	Gestational age (GA)range 10 to 40 weeks (average 30.6 weeks) Various swabs used including vaginal, endocervical, anorectal, perianal, urethra and urine 7/9 studies used selective media	18% antenatal (mean) 20% intrapartum (mean)	Range 42.8% to 100% (False negative rate range 0% to 57.2%)	Range 49% to 100% (False positive rate 0% to 51%)	**Overall:** mean 69% (range 43% to 100%) **Prospective studies only (7 studies):** Mean 63.3%, median 61% (range 46% to 89%) *Screening before 35 weeks' GA:* mean 58.5% *Screening after 35 weeks' GA:* mean 70.2% **Retrospective studies only (2 studies):** mean 74.9%	**Overall:** mean 94% (range 80% to 100%) **Prospective studies only (7 studies):** Mean 94.2%, median 95% (range 87% to 97%) *Screening before 35 weeks' GA:* mean 93.0% *Screening after 35 weeks' GA:* mean 95.2% **Retrospective studies only (2 studies):** mean 92.9%	The 100% PPV/NPV figures came from small studies (all <66 participants) so should be interpreted cautiously Unclear how pooled figures calculated

Author and year	Country; number of women	Swabs	Prevalence	Sensitivity for carriage in labour	Specificity for carriage in labour	PPV for carriage in labour	NPV for carriage in labour	Comments
						(range 43% to 100%) *Early screening:* mean 63.5% *Late screening:* mean 93.2%	(range 80% to 100%) *Early screening:* mean 90.2% *Late screening:* mean 97.5%	
Kovavisarach 2008[23] (Likely to have been excluded from Valkenberg systematic review as not clear if antibiotics taken in pregnancy)	Thailand n=360 (83.9% successfully cultured at both time points and analysed)	GA 35-37 weeks Lower vagina and anorectum swabs Selective media Both tests were performed in the same hospital	13.1% antenatal 13.6% intrapartum	70.7% (False negative rate 29.3%)	95.4% (False positive rate 4.6%)	70.7%	95.4%	No neonates showed signs or symptoms of EOGBS. Unclear if any antibiotic usage between antenatal screening and delivery
Towers 2010[24]	USA n=1,507	Late 3rd trimester	15.4% antenatal	51% (False	94% (False	67%	88%	Some physicians/ laboratories did

Author and year	Country; number of women	Swabs	Prevalence	Sensitivity for carriage in labour	Specificity for carriage in labour	PPV for carriage in labour	NPV for carriage in labour	Comments
	(97.7% analysed)	Women with swabs from before 35 weeks' gestation and more than 6 weeks before delivery were excluded Intrapartum swabs were taken from the vaginal introitus and perianal area, and cultures performed using selective media IP tests were performed in one hospital,	20.1% intrapartum	negative rate 49%)	positive rate 6%)			not follow CDC recommended procedures for the AN GBS testing e.g. most (84%) did not routinely swab transrectally; 48% did not use the specified transport medium for swabs; only 2/6 laboratories used the recommended selective broth media before plating 66 women (4.5% of those analysed) had AN swabs earlier than 35 weeks, and

Author and year	Country; number of women	Swabs	Prevalence	Sensitivity for carriage in labour	Specificity for carriage in labour	PPV for carriage in labour	NPV for carriage in labour	Comments
		but AN tests were performed by 25 different clinics Methods used for the AN culture varied (see comments)						6.3% were cultured after 37 weeks No cases of EOGBS were identified in the study
Lin 2011[22]	USA n=5,497 (85.4% successfully cultured at both time points and analysed)	Methods for AN testing not specified, reported to be performed by various healthcare providers and laboratories during routine care Among	24.5% antenatal 18.8% intrapartum	67.0% (calculated) (False negative rate 33%)	84.8% (calculated) (False positive rate 15.2%)	50.5% overall 60.6% for culture at GA 35-37 weeks	91.7% overall 89.5% for culture at GA 35-37 weeks	Prospective Only women ≥32 weeks at delivery included 2 newborns (0.36/1,000 births) developed EOGBS, one whose mother had been negative AN, one had not

Author and year	Country; number of women	Swabs	Prevalence	Sensitivity for carriage in labour	Specificity for carriage in labour	PPV for carriage in labour	NPV for carriage in labour	Comments
		women for whom timing of AN swab was recorded (67.9%): 75.7% 35-37 weeks' GA; 12.5% at <35 weeks; 11.8% at ≥38 weeks IP testing was at ≥32 weeks Vaginal rectal swabs Selective media IP testing was performed at 3 hospitals using the same						been swabbed AN or IP, neither received antibiotics. Both were treated and survived. Proportion receiving antibiotics in pregnancy was similar in women who were positive antenatally but negative IP (18.6%), and those who were positive AN and IP (15.2%; p=0.29)

Author and year	Country; number of women	Swabs	Prevalence	Sensitivity for carriage in labour	Specificity for carriage in labour	PPV for carriage in labour	NPV for carriage in labour	Comments
		protocol						

Rapid tests

The length of time needed to perform culture tests, and the potential for GBS status to change between testing and labour has prompted interest in rapid tests that can be performed at the onset of labour, and provide results swiftly enough to guide management during labour. The accuracy of these methods has been tested against intrapartum culture methods. In this context, test accuracy is a standard diagnostic accuracy assessment, where the new and gold standard tests are carried out at the same time. In this context:

- Sensitivity refers to the ability of the rapid intrapartum test to identify women who are colonised with GBS at the time of labour based on intrapartum culture based testing
- False negatives refer to women who screen negative for GBS carriage on the rapid intrapartum test but who are positive for GBS carriage on intrapartum culture based testing
- The positive predictive value (PPV) refers to the proportion of women with positive rapid intrapartum tests that are positive for GBS carriage by intrapartum culture based testing
- Specificity refers to the ability of the rapid intrapartum test to identify women who are not colonised with GBS at the time of labour based on intrapartum culture based testing
- False positives refer to women who screen positive for GBS carriage on the rapid intrapartum test but who are negative for GBS as determined by intrapartum culture based testing
- The negative predictive value (NPV) refers to the proportion of women with negative rapid intrapartum tests that are negative for GBS carriage by intrapartum culture based testing

Diagnostic accuracy (analytical validity) studies cannot determine whether a newer test is better than the current reference standard. However a newer test may be shown to perform better than the current reference standard test in terms of clinical validity (how well it predicts a clinical outcome) or clinical utility (whether its use improves clinical outcomes). The new test may also still be preferred if it offers other advantages. For example, the rapid tests for GBS may be preferred if they allow testing to take place at the time of admission for labour.

It is feasible that PCR based techniques could have greater sensitivity for picking up low levels of GBS colonisation than culture based techniques, but they may also be more prone to false positives. Also, whether any additional low level colonisations detected by PCR but not culture have clinical relevance would need to be established. Ideally the accuracy of these new tests for predicting newborn GBS colonisation or EOGBS would be assessed as well as the accuracy compared with intrapartum culture.

A Health Technology Assessment (HTA) carried out a systematic review (search date 2005) assessing the accuracy of rapid GBS tests used in women in labour.[17] This HTA was in press at the time of the previous update of NSC screening policy, and was considered as part of that report. It is described briefly here to provide context for subsequent studies.

The HTA review included 29 studies; these studies were generally considered to be of poor quality and reporting. It found that the most accurate and rapid tests were real time PCR and optical immunoassay (OIA; see Table 4 for results). The number of studies assessing these

techniques which were pooled to obtain the meta-analytical result was low (2 for PCR, 1 for OIA), as was the number of participants (914 for PCR, 1,340 for OIA).

The HTA also performed a primary study assessing the accuracy of PCR and OIA for intrapartum GBS testing.[17,18] It found that PCR was more accurate than OIA ($p<0.01$), and that the greatest sensitivity came from combining results from both vaginal and rectal swab tests (see Table 5 below for results). Women with a positive PCR test were significantly more likely to have neonates with GBS colonisation as determine by ear swab (OR 29.4, 95% CI 15.8 to 54.8; $p<0.001$). The accuracy for the rapid tests in this study was generally lower than in previous studies. Pooling its results with those of its meta-analysis gave PCR a sensitivity of 90% and specificity of 92%, and OIA a sensitivity of 63% and specificity of 79%. It concluded that neither real time PCR or OIA was accurate enough to be recommended for routine use.[17]

The study also looked at how well the presence of maternal risk factors for GBS predicted maternal colonisation as identified by intrapartum culture. It found that the presence of ≥1 maternal risk factor was not a sensitive predictor of maternal colonisation (30%), with PCR significantly more sensitive and specific ($p<0.001$; see Table 4 for results).[18] Presence of maternal risk factors for GBS was also not significantly associated with neonatal GBS colonisation (OR 1.44, 95% CI 0.80 to 2.62; $p=0.2$). However, mothers with risk factors would have been more likely to be given intrapartum antibiotics (in accordance with existing RCOG guidelines), and this may have influenced these results. Use of intrapartum antibiotics was controlled for in the analysis, but nonetheless the authors noted that the true relationship between risk factors and neonatal colonisation could not be determined.

As the main advantage of rapid tests is that they could potentially be used at the time of labour, for this report we only included studies assessing their use in labour. We only included studies which used intrapartum culture as the reference standard, and that used selective broth culture followed by subculture for GBS detection, as this is the method suggested by the US CDC and UK HPA. As real time PCR and OIA were found to be the most accurate and rapid methods in the HTA,[17] these are the methods assessed here.

No additional OIA studies met inclusion criteria (see Methodology – Quality section). Five additional studies of PCR published since 2008 met inclusion criteria.[30-34] All of these papers utilised real time PCR for GBS detection, three used the IDI-Strep assay, and three used the Xpert GBS test (one study used both). The IDI-Strep Assay has US FDA approval for use in GBS testing, and can be used intrapartum, providing results within about 1 hour.[35] However, it requires manual sample preparation before the PCR. The Xpert GBS test has automated sample preparation for the PCR, and takes about 75 minutes in total to obtain results.[36] The Xpert GBS test also reportedly does not need to be run in batches, which means that tests could be performed as needed without waiting for a large enough batch of swabs for testing to be collected.[34]

The additional papers[30-34] found that compared to intrapartum culture, rapid intrapartum PCR tests had:

- Sensitivity ranging from 79.3% to 91.1%
- Specificity ranging from 95.4% to 97.6%
- PPVs ranging from 84.2% to 94.2%
- NPVs ranging from 93.7% to 97.4%.

The one study that assessed two PCR tests found that the Xpert GBS assay had greater sensitivity and NPV than the IDI-Strep B assay ($p \leq 0.006$).[34]

One of the most recent papers was of particular interest as it tested the Xpert GBS system in the labour ward, as operated by midwives.[30] This may be representative of how the test would need to be performed if it were to be used in clinical practice, as it would allow 24 hour access to results. It found sensitivity of 85%, specificity of 96.5%, PPV of 85.7%, and NPV of 96.3%. Although it had slightly higher sensitivity than antenatal culture at 35-37 weeks (81%), this was not significantly different. Antenatal culture had a specificity of 95.1%, PPV of 79.7% for GBS carriage in labour and NPV of 95.5% for negative GBS status in labour when compared to intrapartum culture.

In this study results of the PCR were obtained at least 4 hours prior to delivery for 76.5% women overall (regardless of GBS status), i.e. with enough time to give adequate IAP if they were found to be positive. Assuming that time between results and labour does not vary by GBS status, this suggests that about a quarter of GBS positive women would not be able to receive adequate IAP after receipt of their PCR results.

When considering just the women who were GBS positive by intrapartum culture, there was no significant difference in the proportion who would have been able to have adequate IAP based on intrapartum PCR (68.2%) and based on antenatal culture (63.6%; p=0.54).

As for a number of other studies, if the initial PCR did not work it was repeated on a second swab collected at the same time as the first, and those samples that failed two PCRs were considered unresolved. In this study 8.3% of samples were unresolved. If intrapartum PCR was used in practice a strategy would need to be in place to decide how women with unresolved PCR should be treated e.g. whether they should all receive or not receive IAP, or if a risk based approach should be used to decide on IAP provision. The authors note that the number of samples requiring two PCR cycles reduced over the time of the study (from 13% initially to 2% at the end), but the number of unresolved samples remained similar.

Among the three other studies that reported the results of antenatal culture,[31-33] these found:

- Sensitivity ranged from 60.5% to 84.3%
- Specificity ranged from 93.2% to 99.2%
- PPV ranged from 84.4% to 96.3%
- NPV ranged from 87.9% to 92.3%

One study reported the performance of the antenatal test and the intrapartum PCR test to be comparable, although no statistical comparison was presented.[31] Another study reported that sensitivity and NPV were “significantly” better with intrapartum PCR (XpertGBS assay) than with antenatal culture, although no specific statistical comparisons of these figures or p values were provided.[32] None of these additional studies assessed the accuracy of a risk based approach.

Table 4: Results of a systematic review of rapid test accuracy[17,37]

Author, year, included studies	Technique (time taken; number of studies; participants pooled)	Sensitivity (range)	Specificity (range)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Comments
Daniels 2009[17]; Honest 2006[37] Systematic review of 29 studies US, Israel, Canada, UK n=15,691	Real time PCR (40 min; 2 studies; 914 women)	94% to 97%	96% to 100%	38.8 (6.1 to 248.7)	0.06 (0.03 to 0.11)	Studies used various swab sites including vagina, ectocervix, rectum, anal and perianal If results for different swab sites were available, results for vaginal and rectal swabs are reported here. If results for different gold standard culture methods were available, results for selective culture are reported here in preference to results using direct culture. For DNA hybridisation only results from the 1 hour assessment were included. Prevalence of GBS colonisation in these studies ranged from 4.4% to 32%.
	OIA (30 min; 3 studies; 1,340 women)	37% to 72%	96% to 98%	14.7 (10.6 to 20.3)	0.47 (0.31 to 0.73)	
	DNA hybridisation (60 minutes; 1 study; 268 women)	8%	100%	29.9 (1.6 to 566.3)	0.92 (0.83 to 1.01)	
	Enzyme immunoassay (5-10 minutes; 5 studies; 1,948 women)	11% to 39%	99% to 100%	36.3 (10.8 to 122.0)	0.80 (0.70 to 0.92)	
	Latex agglutination (70-82 minutes; 4 studies; 2,095 women)	30% to 92%	93% to 98%	10.4 (3.1 to 34.4)	0.38 (0.07 to 1.96)	
	Islam starch medium (120-1440 min; 1 study; 212 women)	96%	100%	356.3 (22.3 to 5685.8)	0.04 (0.01 to 0.30)	

Table 5: Primary studies published since 2008 assessing the accuracy of intrapartum real time PCR compared with intrapartum culture for detecting GBS

Author and year	Country, number of women	Swabs	Prevalence (by IP culture)	Technique	Sensitivity	Specificity	PPV	NPV	Comments
Daniels 2009[17] Daniels 2011[18]	UK n=1,418 (98.7% provided swabs and analysed)	Vaginal and rectal (assessed individually; if either test positive the result was considered positive) Intrapartum (IP; reference standard)	21.2%	Smart GBS PCR kit (median 80 min to test result) BioStar OIA STREP B kit (median 35 min to test result) Risk factor based Tests performed IP on vaginal swabs	84% 72% 30%	87% 57% 80%	65% 31% 29%	95% 88% 81%	Sensitivity and specificity varied according to presence or absence of maternal risk factors 15 babies had infections immediately after birth, 6 were invasive, and 3 of these were diagnosed with EOGBS. All recovered. PCR tests were carried out in batches, rather than in real time. This meant that results were usually

Author and year	Country, number of women	Swabs	Prevalence (by IP culture)	Technique	Sensitivity	Specificity	PPV	NPV	Comments
									obtained after delivery
Alfa 2010[33]	Canada n=205 (95.6% analysed)	Vaginal-rectal IP (reference standard) and antenatal (AN) swabs AN swabs were reported to be performed routinely at 35-37 weeks (further details not provided)	21.4%	IDI-Strep (*cfb* gene) performed IP	90.5% (60.5% for AN culture)	96.1% (99.2% for AN culture)	86.4% (96.3% for AN culture)	97.4% (87.9% for AN culture)	Average time between sample and delivery 13h 54 min (range 0 min to 5 days 11h 46 min) Sensitivity and specificity of the antenatal test were calculated from figures provided in the paper
Edwards 2008[34]	USA n=1,028 (76.3% analysed) n=548 intrapartum plus 480 antenatal	Vaginal- rectal IP or AN swabs (results pooled as the reference standard)	24%	IDI-Strep Xpert GBS assay (median time from sample collection to results 2.1 hours) The PCR tests were performed at the same	79.3% 91.1%	95.4% 96.0%	84.2% 87.8%	93.7% 97.1%	Antenatal and intrapartum results were pooled as no difference was found in test performance Samples that did not yield a result in the first PCR assay were re-run

Author and year	Country, number of women	Swabs	Prevalence (by IP culture)	Technique	Sensitivity	Specificity	PPV	NPV	Comments
				time as the culture (IP or AN)					The sensitivity and NPV of the Xpert were significantly better than the IDI-Strep B assay (p≤0.006)
Money 2008[31]	Canada n=190 (94.7% completed the study)	Vaginal-rectal IP (reference standard) and AN swabs at 35 to 37 weeks collected as part of usual care AN cultures were reported to be performed by community laboratories and results collected from the patient, the hospital chart, private physician records, and hospital lab records	30%	IDI-Strep B (performed IP) Mean time from sampling to report: 99 min (range 50-255 min). The wide range was attributed to time of day and staffing issues	90.7% (84.3% for AN culture)	97.6% (93.2% for AN culture)	94.2% (86% for AN culture)	96.0% (92.3% for AN culture)	Women planning to have a Caesarean section or with contra-indication to vaginal delivery, <35 weeks GA, with previous GBS infant, GBS bacteriuria in the current pregnancy, HIV, or urgent indication for delivery excluded. Results were available >4 hours before

Author and year	Country, number of women	Swabs	Prevalence (by IP culture)	Technique	Sensitivity	Specificity	PPV	NPV	Comments
									delivery in 81% of cases (i.e. in time to initiate adequate IAP) Two PCRs failed due to inadequate DNA obtained Performance of the PCR test and AN culture were reported to be comparable
Young 2011[32]	USA n=559	Vaginal-rectal IP (reference standard) and AN swabs Results for AN swabs were obtained from the woman's medical records Cultures were reported to be performed according to CDC guidelines at the	23.8%	Xpert GBS assay (performed IP) 99.6% of samples were processed in ≤50 min Median time for a positive result 41 min; for a negative result 48 min; for a PCR error 8 min;	90.8% (reduced to 89.5% if failed PCRs considered to be discordant) (69.2% for AN culture)	97.6% (reduced to 95.3% if failed PCRs considered to be discordant) (96.0% for AN culture)	92.3% (reduced to 85.6% if failed PCRs considered to be discordant) (84.4% for AN culture)	97.1% (reduced to 96.7% if failed PCRs considered to be discordant) (90.9% for AN culture)	Performance of the IP culture was blinded to the results of AN culture and PCR Sensitivity and NPV were reported to be significantly better with IP PCR than the AN culture (p value not

Author and year	Country, number of women	Swabs	Prevalence (by IP culture)	Technique	Sensitivity	Specificity	PPV	NPV	Comments
		certified laboratory of the medical centre conducting the study or two other certified laboratories		for an invalid PCR result 48 min					reported, potentially based on non-overlap of 95% CIs for these measures) Black and Hispanic women were significantly more likely to have discordant culture results (p=0.02) If the first PCR did not work it was repeated, 2.1% of samples ended up with no results
Martinez de Tejada 2011[30]	Switzerland n=758 eligible, 91.7% analysed for diagnostic accuracy;	Vaginal-rectal IP (reference standard) and AN swabs (35-37 weeks) Swabs were reported to be	19.3%	Xpert GBS assay performed IP by midwives in the labour ward Results of the	85.0% (AN culture 81.0%)	96.5% (AN culture 95.1%)	85.7% (AN culture 79.7%)	96.3% (AN culture 95.5%)	Among the 63 eligible women not tested, 80% were not tested due to admission in advanced labour, and

Author and year	Country, number of women	Swabs	Prevalence (by IP culture)	Technique	Sensitivity	Specificity	PPV	NPV	Comments
	73.5% for feasibility	collected in a uniform manner following CDC recommendations Selective media was used for cultures		PCR were obtained at least 4h prior to delivery for 76.5% women					20% due to high workload. If the first PCR did not work it was repeated; 8.3% of tests were unresolved Sensitivity of the IP PCR and AN culture were not significantly different (p=0.72) Agreement between IP PCR and culture was not affected by the status of the membranes

AN antenatal, IP intrapartum

As well as test accuracy there are also a number of practical issues around the use of rapid testing that would need to be considered, including that the test would ideally need to give results early enough in labour to allow administration of the recommended duration of intrapartum prophylaxis, and to be available around the clock.

One of potential drawbacks of using the existing real time PCR assays intrapartum to direct IAP is that they are not be able to determine antimicrobial susceptibility. Tests of antimicrobial susceptibility may help to guide choice of antibiotic in women who are allergic to penicillin. In the US, the CDC recommends antimicrobial sensitivity testing of antenatal GBS isolates from women who are allergic to penicillin and at high risk of anaphylaxis. Its recommended sensitivity testing methods are culture based and could not be carried out in sufficient time to guide antibiotic selection during labour if colonisation was only identified by rapid testing once labour was underway.

The CDC say that if a rapid test is to be clinically useful during labour, it needs to be a simple test that can be performed at the bedside by the labour and delivery staff, with results ready in under 30 minutes, and sensitivity and specificity of 90% or over compared to intrapartum culture testing. Ideally it should also be able to detect mutations that confer antibiotic resistance. As yet, rapid PCR testing does not meet all of these criteria.

Although rapid testing in labour may be a better indicator of GBS colonisation status at the time of labour than screening at 35 to 37 weeks, it would still be the case that the majority of women identified by screening would not go on to have an infant with EOGBS. This is because a considerable proportion of pregnant women are colonised with GBS at the time of labour (about 21% in the UK), but only a very small proportion of infants develop EOGBS (less than 0.05% of livebirths in the UK).

Summary: Criterion 5 Not Met

The current standard method of identifying GBS colonisation in pregnant women is based on culture of vaginal and rectal and vaginal swabs. As this culture method is the current standard method of detection, there is nothing to which it can be compared to determine its true analytical accuracy.

Due to the time taken to obtain results using this method (around 3 days excluding transport time) and to accommodate the potential for changes in carriage status over time, screening is usually done between 35 to 37 weeks' gestation in countries that recommend universal screening. However, antenatal culture results do not perfectly predict culture results for swabs taken at the time of labour and delivery, in part because colonisation status is thought to vary. The studies identified focused on the performance of antenatal culture for predicting intrapartum GBS colonisation, rather than for predicting EOGBS.

One systematic review assessing the accuracy of culture based antenatal screening to predict GBS carriage in labour identified nine relevant studies in just under 9,000 women. It found that on average about 70% of women who test positive for GBS on antenatal screening after 35 weeks of pregnancy also test positive during labour, while on average about 95% of women who test negative on antenatal screening after 35 weeks of pregnancy also test negative during labour.

The largest subsequent study (n=5,497) looking at the same aspect of performance of the test in routine clinical practice in the US found that 50.5% of women who tested positive for GBS on antenatal screening also tested positive during labour, while 91.7% of women who tested

negative on antenatal screening also tested negative during labour. This means that 49.5% of the women testing positive on screening would be treated with IAP despite not being GBS positive at the time of labour (over treatment). Also, 8.3% of women testing negative on screening would not be treated with IAP despite being GBS positive at the time of labour (under treatment). The study found that some women were not screened at the recommended time period (35 to 37 weeks). Looking at only the women who were screened at the recommended time, 60.6% of women who tested positive for GBS on antenatal screening also tested positive during labour, while 89.5% of women who tested negative on antenatal screening also tested negative during labour.

Due to the limitations of antenatal GBS screening, there is interest in developing rapid testing methods that can be used intrapartum, to detect GBS colonisation status at the time of labour. Real time PCR appears to be the most promising of these methods, with a systematic review and meta-analysis carried out as part of a UK HTA finding a pooled sensitivity of 90% and specificity of 92% compared to intrapartum culture. Studies published since 2008 have found sensitivities for the rapid intrapartum test ranging from 79.3% to 91.1%, specificities ranging from 95.4% to 97.6%, PPVs ranging from 84.2% to 94.2%, and NPVs ranging from 93.7% to 97.4%.

One study of particular interest used a real time PCR system operated in the labour ward by midwives. This type of system is likely to be the most practical way to ensure that rapid testing would be available at all times, and not require specialist operators. It found sensitivity of 85%, specificity of 96.5%, PPV of 85.7%, and NPV of 96.3%. In this study intrapartum PCR and antenatal culture did not differ in their sensitivity when compared to intrapartum culture, but another study found that real time intrapartum PCR was more sensitive than antenatal culture.

Overall, real time PCR shows promise for potential intrapartum use on the labour ward, but has some disadvantages, for example that the tests currently available cannot determine antibiotic sensitivity to direct choice of antibiotic in women who are allergic to penicillin. In addition, the method has not been sufficiently studied in this setting to be ready for widespread use.

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

2008 update report: *"The result of any screening test is either GBS positive or negative."*

Criterion 6 Not Applicable

7. The test should be acceptable to the population

2008 update report: *"Within a UK population recent work has suggested a high rate of refusal to take part in a study assessing the value of rapid intrapartum screening for GBS carriage. This is not the same as declining to participate in a routine screening programme, but the responses of women who decline to take part illustrates some of the issues with introducing screening. From a total population of 3000 women approached to participate, 57% declined. The reasons for declining were not given by 44% of these women, but of the remainder reasons included objections to the swabs (16.7%), wanting to avoid added intervention (4%) and family pressures to refuse (2%). There was also a strong association between declining to participate and ethnicity, with women from Asian backgrounds being particularly likely to decline to participate.*

For women who did participate in the study the taking of the swabs was generally acceptable, although more women found the taking of the rectal swab unpleasant compared with the vaginal swab."

The update search identified no additional studies assessing the acceptability of GBS screening in pregnancy in the UK. The search did identify an additional publication from the UK HTA described by the 2008 update report above.[18] It reported that among the women who did agree to participate in the trial of intrapartum screening, there was a high level of satisfaction with the process, with 80.5% satisfied or very satisfied with the information provided, 94.3% happy or very happy with the way the swabs were taken, and 94.1% were confident in its use in routine care. However, as the swabbing procedure is only one aspect of what would occur with routine screening, and in this HTA the results were not used to guide care, it is not clear whether the women would have showed the same responses to a routine screening programme that might result in the need for intravenous antibiotic treatment in labour.

The search also identified one study relating to one aspect of the acceptability of screening in the Republic of Ireland.[38] The study included 600 pregnant women and compared the efficacy of self and physician collected vaginal rectal swabs and assessed women's preference.

A higher proportion of women stated that they would prefer a health professional to collect their swab (43.2%), than stated that they would prefer to collect their own swabs (28.5%), or expressed no preference (28.3%). Similarly a higher proportion (45.2%) would recommend to a friend that a health professional took their swabs, while 26.5% would recommend self-swabbing, and 28.3% had no preference. The most common reason women reported for response was that they felt they might not take the swab properly. The authors suggested that a follow up study was needed to assess whether women's preferences would change if they knew that the study found self and health professional collected swabs showed a high level of agreement for detecting GBS (97.5%).

In the US the CDC recommended universal screening in 2002. A paper looking at data collected by the CDC's Active Bacterial Core surveillance system found that 85% of pregnant women were screened for GBS in pregnancy between 2003 and 2004.[39] A similar proportion (85.1%) of those who had an indication for IAP received it in this period.

Summary: Criterion 7 Uncertain

No additional studies since the last update have assessed the acceptability of the GBS test to pregnant women in the UK. One study from the Republic of Ireland suggested that women would generally prefer health professionals to take their swabs, rather than take them themselves. The US has implemented universal GBS screening and one study suggested a high level of uptake of screening (85% of pregnant women) between 2003 and 2004.

8. 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

2008 update report: *"There are no further diagnostic tests offered to women with a positive test result. Antenatal treatment of a positive test result does not eradicate GBS carriage and therefore does not prevent the need for IAP"*

Summary: Criterion 8 Not Met

This remains unchanged. This means that all women identified as carrying GBS in pregnancy would be offered IAP, despite the risk of having an infant with EOGBS being low. Additional ways of determining which GBS colonised women are most at risk of having an infant with EOGBS could help to reduce the number of women who would need to be treated with IAP.

9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

Criterion 9 Not Applicable

10. 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

2008 update report: *"In a Cochrane review of five RCTs (all of poor quality), [intrapartum antibiotic prophylaxis (IAP)] was found to decrease rates of culture proven EOGBS neonatal sepsis from approximately 5% to 0.2% (a relative decrease of 83%, 95%CI 61% to 93%). In a recent HTA funded modelling study of screening for GBS carriage in pregnancy, a separate meta-analysis was undertaken using different selection criteria and utilising a Bayesian approach, which suggested the effectiveness was a relative risk reduction of approximately 99.97%, 95%CI 99.88% to 100%.*

However, approximately half of all neonatal sepsis is 'presumed' i.e. in only half of all cases of clinical neonatal sepsis is the infecting organism isolated on culture from a normally sterile site (usually blood or CSF). Therefore measuring only culture-proven GBS sepsis will underestimate the incidence of all sepsis due to GBS. Just as it will underestimate the incidence of any specific cause of sepsis such as E. coli. In addition, if a woman receives penicillin during labour and her baby then becomes ill with sepsis, it is more likely that GBS will not be isolated because of the antibiotic contained within the blood even though GBS may be causing the babies illness."

"As no randomised trials have measured the effect of IAP on the incidence of neonatal sepsis as a whole (proven and presumed) or on neonatal death, it is not possible to accurately quantify the effectiveness of IAP at decreasing the incidence of EOGBS sepsis.

IAP therefore appears to be effective in preventing EOGBS sepsis, but the existing evidence from randomised trials probably over-estimates the magnitude of this effectiveness."

Intrapartum antibiotic prophylaxis

Intrapartum antibiotic prophylaxis is the mainstay of EOGBS prevention. The update search identified no additional RCTs of intrapartum antibiotic prophylaxis (IAP). The only additional study identified was a Cochrane systematic review re-analysing data from existing RCTs of intrapartum antibiotics for known GBS colonisation.[40]

The new systematic review[40] updated the previous Cochrane review.[41] Unlike the original review, the updated review did not focus on the outcome of infant colonisation with GBS. The updated review's primary outcome was neonatal mortality, and it excluded RCTs that only looked at infant GBS colonisation. It included 4 RCTs in 852 women (Boyer 1986, Edwards 2002, Matorras 1990, and Tuppurainen 1989). Two RCTs compared ampicillin versus no treatment,

one compared penicillin versus no treatment, and one compared ampicillin versus penicillin. The quality of these studies was reported to be poor and the risk of bias high. The review excluded two RCTs included in the earlier review: one because it only looked at the outcome of colonisation, the other because it was not truly randomised.

Only one RCT (of ampicillin) looked at the review's primary outcome of infant mortality. It found no significant effect of intrapartum antibiotics on all cause neonatal mortality, neonatal mortality from GBS, or neonatal mortality from infections caused by bacteria other than GBS, compared with no treatment (see Table 6 below for results). Intrapartum antibiotics reduced the risk of culture confirmed early and probable early GBS infection (at age less than 7 days). Probable GBS infection was defined as symptoms and signs of sepsis or pneumonia in a neonate born to a GBS positive mother, and bacterial cultures from normally sterile body fluids obtained from the neonate that were negative for GBS. The previous Cochrane review looked at the outcome of EOGBS sepsis, but did not define this or look at the outcome of probable GBS sepsis.

The updated review found that IAP did not significantly reduce late onset GBS infection (at age 7 days or later) or infective outcomes relating to non-GBS bacteria, or improve maternal outcomes compared to no treatment (see Table 6). No significant differences between penicillin and ampicillin for any outcome were found by the one RCT (352 participants) that made this comparison.

Based on the limited amount and quality of RCT evidence available, the review concluded that giving intrapartum antibiotics is not supported by conclusive evidence. They note that performing new, adequately sized double blind RCTs may not be possible now that practice guidelines recommending the use of intrapartum antibiotics have been introduced in many areas.

Table 6: Results of a systematic review of intrapartum antibiotic prophylaxis in women with known GBS colonisation

Outcome	Result	Number of RCTs
Outcomes improved by intrapartum antibiotic prophylaxis (IAP)		
Culture confirmed early GBS infection	AR 0.4% with IAP vs. 4.7% with no treatment RR 0.17, 95% CI 0.04 to 0.74 ARR 4%, 95% CI 1% to 7% NNT 25, 95% CI 14 to 100	3 (488 infants)
Probable early GBS infection	AR 0.7% with IAP vs. 5.7% with no treatment RR 0.17, 95% CI 0.03 to 0.91 ARR 5%, 95% CI 1% to 9% NNT 20, 95% CI 11 to 100	2 (324 infants)
Outcomes not improved by intrapartum antibiotic prophylaxis (IAP) (no significant difference to no treatment)		

Outcome	Result	Number of RCTs
All cause neonatal mortality	RR 0.19, 95% CI 0.01 to 3.82	1 (164 infants)
Neonatal mortality from GBS	RR 0.31, 95% CI 0.01 to 7.50	1 (164 infants)
Neonatal mortality from non-GBS bacterial infections	RR 0.31, 95% CI 0.01 to 7.50	1 (164 infants)
Late onset GBS	RR 0.36, 95% CI 0.01 to 8.69	2 (289 infants)
Neonatal sepsis, meningitis, urinary tract infection or pneumonia due to bacterial organisms other than GBS	RR 1.00, 95% CI 0.15 to 6.79	2 (289 infants)
Maternal sepsis in the peri/postpartum period	RR 0.31, 95% CI 0.01 to 7.49	1 (160 women)
Maternal puerperal infection	RR 0.16, 95% CI 0.01 to 3.03	1 (121 women)

Antenatal oral antibiotic treatment

The update search identified one small RCT of oral antibiotic treatment in 32 pregnant women found to be colonised with GBS on screening at 35-37 weeks.[42] The study had calculated that with 32 participants and a 25% dropout rate it would have power to detect a reduction in the rate of colonisation at delivery from and expected 72% to 8.5% (their estimate of the rate of naturally acquiring GBS between 35-37 weeks and delivery).

It found that antenatal oral amoxicillin (1g daily for 5 days after enrolment) did not significantly reduce GBS colonisation at the time of labour compared with placebo (42.9% with amoxicillin vs. 66.6% with placebo; p=0.20). There was also no difference in the proportion of neonates admitted to ICU (6.3% with amoxicillin vs. 18.8% with placebo; p=0.29). One of the neonates admitted to ICU from the placebo group had presumed sepsis, and one in the amoxicillin group had culture diagnosed GBS sepsis.

Vaginal cleansing in labour

As GBS can be passed on during delivery, there has been interest in the possibility that applying a disinfectant to the vagina during labour may reduce transmission. A Cochrane systematic review that assesses the effects of vaginal chlorhexidine during labour in women with GBS colonisation to prevent EOGBS had its most recent update published in 2008 (update search 2007).[43] It identified no additional studies, and its conclusions remained unchanged. These were that vaginal chlorhexidine reduces GBS colonisation of the infant in the first seven days of life (3 RCTs, 328 participants; RR 0.72, 95% CI 0.56 to 0.91), but does not significantly reduce GBS sepsis, GBS pneumonia, GBS meningitis, or mortality.

One additional large RCT and another RCT of chlorhexidine were identified.[44,45]

The larger of the RCTs compared 0.5% chlorhexidine vaginal wipes during labour plus full 0.5% chlorhexidine body washes for the infant at birth versus water vaginal wipes in labour plus a 0.5% chlorhexidine foot wash for the infant at birth (control).[44] The RCT was carried out in South Africa where maternal antenatal GBS screening is not routinely carried out. It did not require that women should be colonised with GBS for inclusion in the trial, and determined vaginal colonisation in a sample of women after randomisation. The trial randomised 8,011 women and

their neonates; and GBS tests were carried out on 3,964 mother-neonate pairs (only vaginal deliveries). Among the women tested 20.9% showed vaginal colonisation with GBS.

Early onset sepsis was the primary outcome and was defined as culture confirmed or clinical sepsis occurring in the first three days of life; late onset sepsis referred to culture confirmed or clinical sepsis occurring between 3 and 28 days after birth. The RCT found chlorhexidine did not reduce rates of early onset neonatal sepsis compared with control (3.5% with chlorhexidine vs. 3.6% with control; p=0.65). GBS was the most commonly identified bacteria found in sterile sites in early onset sepsis (57% of those cultured). Chlorhexidine also did not reduce late onset sepsis (<1% in both groups; p=0.43).

Chlorhexidine also did not reduce neonatal colonisation with GBS (another primary outcome) compared with control (54% with chlorhexidine vs. 55% with control; efficacy [% change in the number of cases in the control group with chlorhexidine] was -0.05%, 95% CI -9.2% to +7.9%).

The rate of neonatal death was lower in the chlorhexidine group (8.3 per 1000 births) than in the control group (12.8 per 1000 births; p=0.0490). This effect was largely observed in the first hours after birth, when the most common cause of death was birth asphyxia. This, and the lack of effect of the intervention on the primary outcomes, led the authors to suggest that this effect was unlikely to be due to the chlorhexidine intervention.

The second RCT included 5,008 women in labour in Pakistan, and compared chlorhexidine vaginal and neonatal wipes versus placebo.[45] It found no difference in neonatal mortality or sepsis within 7 days of birth between the groups (RR 0.91, 95% CI 0.67 to 1.24).

Summary: Criterion 10 Partly Met

Systematic reviews and RCTs published since 2008 do not change the view that oral antenatal antibiotics and vaginal cleansing with chlorhexidine during labour do not have a place in the prevention of EOGBS.

No additional RCTs assessing the effects of intrapartum antibiotic prophylaxis (IAP) on EOGBS have been published since the last NSC update report. An updated systematic review confirmed that the existing RCT evidence shows a reduction in the risk of culture confirmed and probable early GBS infection with IAP. However, IAP was not shown by these RCTs to reduce neonatal mortality from GBS or from all causes. In addition, these RCTs were small, with none of the meta-analyses including more than 500 women, and of poor quality. This led the authors to conclude that giving IAP to women colonised by GBS is not supported by conclusive evidence, and that better quality studies are needed.

In the context of this uncertainty, and based on the existing evidence and expert consensus, IAP is recommended by US and UK bodies for reducing EOGBS risk in pregnancies identified as being at risk via screening or risk based approaches.[1,3,46]

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

2008 update report: *"There are guidelines for the management of GBS in pregnancy produced by the Centres for Disease Control (CDC) in the USA and guidelines by the Royal College of Obstetricians and Gynaecologists (RCOG) in the UK."*

The CDC released revised guidance in 2010.[1] This guidance continued to recommend universal antenatal GBS screening at 35-37 weeks and IAP provision for all those found to be colonised. There were some changes including a change in the recommended dose of penicillin G for IAP and in the regimens for women allergic to penicillin, updated screening and treatment algorithms for women in preterm labour or with preterm rupture of membranes. The current CDC guideline recommends penicillin G regimen for GBS colonised women is 5 million units intravenously followed by 2.5 to 3 million units intravenously every 4 hours. They report that the optimal timing for IAP is at least four hours before delivery. The CDC guidance also makes recommendations about secondary prevention of EOGBS in infants, including guidance about which infants require evaluation, antibiotic therapy, and observation, based on both signs in the infant and maternal risk factors (including antenatal GBS colonisation) and treatment.

The Royal College of Obstetricians and Gynaecologists' guideline from 2003 is still in place, but is currently under review.[3] The 2003 guideline does not recommend routine antenatal screening for GBS. Instead it recommended offering/considering/discussing IAP in women with specified risk factors for EOGBS:

- Women with a previous baby with neonatal GBS disease (offer)
- Women with GBS bacteriuria in the current pregnancy (consider)
- Women with an incidental finding of vaginal GBS colonisation in the current pregnancy (consider)
- Prematurity < 37 weeks, prolonged rupture of membranes > 18 hours, fever in labour > 38°C (discuss).

The recommended IAP regimen is penicillin G 3g intravenously followed by 1.5g every 4 hours during labour. Intravenous clindamycin 900mg every 8 hours is recommended for women allergic to penicillin. The guideline also addresses management of the newborn infant, although they noted that the evidence base on which to base treatment decisions for newborn infants at that time was weak.

The draft revised RCOG guidelines do not differ largely from the original guidelines. Universal swab-based screening for GBS is still not recommended. The wording regarding how presence of risk factors relates to decisions about IAP has been altered, in most cases moving towards a more definite offer of IAP rather than suggesting that it is considered or discussed. The exception is women in preterm labour where the guideline says that IAP should not be offered if the woman has intact membranes and no other risk factors for GBS. These changes are summarised below:

- Women with a previous baby with neonatal GBS disease (2003: offer; consultation draft: unchanged)
- Women with GBS bacteriuria in the current pregnancy (2003: consider; consultation draft: offer)
- Women with an incidental finding of vaginal GBS colonisation in the current pregnancy (2003: consider; consultation draft: offer)
- Prematurity < 37 weeks (2003: discuss; consultation draft: do not offer IAP in women presenting in preterm labour with intact membranes with no other risk factors for GBS)
- Prolonged rupture of membranes > 18 hours (2003: consider; consultation draft: offer)

- Fever in labour > 38°C (2003: discuss; consultation draft: offer).

NICE antenatal care guidance from 2008 did not recommend universal screening for GBS as evidence of its clinical and cost effectiveness remained uncertain.[47] Draft NICE guidance on the use of antibiotics for the prevention of early onset neonatal infections (in the first 72 hours after birth) is currently out for public consultation.[46] Its draft recommendations are that IAP with benzylpenicillin (penicillin G) should be offered to women with:

- GBS colonisation, bacteriuria or infection during the current pregnancy
- A previous baby affected by invasive Group B streptococcal disease
- Preterm labour with ruptured membranes.

This guideline also addresses management in the newborn.[46] The guideline does not make recommendations on whether or not antenatal screening for GBS should be offered, as this was covered in NICE antenatal care guidance from 2008. It recommends that research should be carried out to determine clinical and cost effectiveness of IAP targeting GBS and guided by routine antenatal screening.

A recently published study reported that there was a lack of evidence and no consensus regarding the management of newborns at-risk of EOGBS, particularly offspring whose mothers had risk factors and were not treated with intrapartum prophylaxis.[48] In light of this the study analysed local guidelines from UK neonatal units about the management of well, term newborns at risk of EOGBS in 2009-10. It found that there was variation in every aspect of management in the 125 guidelines they assessed from 157 neonatal units (71.4% of all units in the UK). This included variation in how maternal risk factors were defined; whether two or four hours were considered adequate intrapartum antibiotic prophylaxis; in what circumstances to give antibiotic treatment to a well, term newborn; and which antibiotic to use.

This study's survey of local neonatal unit guidelines preceded the NICE draft guideline on the use of antibiotics for the prevention of early onset neonatal infection.[46] This includes draft recommendations to guide when a newborn with or without red flag symptoms and/or risk factors should be given antibiotics, which antibiotics to use, and the duration of antibiotic treatment. The final NICE guideline is currently scheduled to be published in August 2012.

Summary: Criterion 11 Partly Met

Guidance from the RCOG and NICE guidance on antenatal care do not currently recommend universal screening.[3,47] The guideline from RCOG and a draft guideline from NICE on prevention and treatment of neonatal infections recommend a risk based strategy to determine which women should be offered intrapartum antibiotic prophylaxis.[3,46] The draft NICE guidance addresses management of newborns, as did the RCOG guideline. The RCOG guideline highlights the lack of evidence in this area.[48]

A recent UK study found that there was variation in local neonatal unit guidelines about the management of well, term newborns at risk of EOGBS in 2010. This was suggested to be due in part to the lack of evidence and national consensus guidelines. More recently, draft NICE guidance on the use of antibiotics for the prevention of early onset neonatal infection has been developed and put out for public consultation. Publication of the final NICE guideline in 2012 may reduce variation in practice.

12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

2008 update report: *"Current practice regarding screening and intrapartum management of GBS in the UK was assessed in 1999 and 2001 by a survey of all obstetric units and more recently in 2007 by a survey conducted by the Royal College of Obstetricians and Gynaecologists and the London School of Hygiene and Tropical Medicine."*

A publication based on the 2007 survey described in the previous NSC update report,[49] as well as another study looking at the use of IAP in women with risk factors in the UK were identified. [9] In addition a study of local neonatal unit guidelines about the management of well, term newborns at risk of EOGBS was identified.[48]

The publication describing the results of the 2007 survey are summarised briefly here as they were covered in the previous update.[49] This audit of all 227 UK maternity units in 2005 found that of the 177 units that responded, 2% had no protocol for the prevention of EOGBS, and protocols covering 171 units (97%) were received.[49] Most of the units (78%) had protocols that recommended a solely risk-based prevention strategy, similar to the 2003 RCOG guidelines. The other 22% recommended a risk and bacteriological testing based approach to offering IAP, with women with some risk factors offered IAP without a bacteriological test, but women with other risk factors recommended a bacteriological test and only those testing positive for GBS being offered IAP. None of the protocols recommended universal bacteriological screening. Over half of the protocols (56%) cited the RCOG guidelines, but only 20% of the protocols fully matched the 2003 RCOG guidelines. The audit noted that the discrepancies might result in some high risk women not receiving IAP, while some women without risk factors receiving IAP needlessly.

The second UK study assessed the presence of risk factors in mothers of 48 EOGBS cases recorded by neonIN surveillance between 2004 and 2007.[9] It found that 67% of mothers had one or more risk factors, and 44% had two or more risk factors. Of the women with at least one risk factor, 18.8% received IV intrapartum antibiotic prophylaxis (IAP) with an antibiotic that GBS was susceptible to (considered as adequate IAP); 9.4% arrived at hospital with insufficient time for IAP; 12.5% had inadequate IAP (oral erythromycin), and 59.4% had no IAP. The women who received antibiotics received benzylpenicillin (33.3%, 2 women), clindamycin (33.3%, 2 women), co-amoxyclav (16.7%, 1 woman), or a cephalosporin plus metronidazole (for possible chorioamnionitis, 16.7%, 1 woman).

The study concluded that despite the existence of the 2003 RCOG guidelines on GBS prevention they had not yet been translated into significant use of IAP in women with risk factors for EOGBS. Based on the assumption that IAP is 80% effective, the study estimated that giving IAP to all the women with one or more risk factors who arrived at hospital in time for adequate IAP may have prevented 48% of the EOGBS cases; giving IAP to all women with two or more risk factors might have prevented 29% of EOGBS cases.

The RCOG 2003 guidance recommends that IAP is "offered", "considered", or "discussed" with specific risk groups. Therefore assessing simply whether women with risk factors do or do not receive IAP may not indicate whether there has been compliance with this guidance.

As noted in Criterion 11, a recently published study noted that there was variation in the content of local guidelines and protocols from UK neonatal units about the management of well,

term newborns at risk of EOGBS in 2009-10.[48] This suggests that practice has not yet been optimised in this area.

NICE has subsequently release draft guidance on the use of antibiotics for the prevention of early onset neonatal infection.[46] Once the final NICE guideline is released this may reduce variation in practice in this area.

Summary: Criterion 12 Partly Met

There is some evidence that clinical management and treatment of pregnant women based on risk based assessment may not yet be optimised. Studies from the UK up to 2007 suggest that not all women with risk factors for GBS receive IAP. It is not clear whether the women with risk factors who did not receive it had it "offered" to, "considered" for, or "discussed" with them in accordance with the 2003 RCOG recommendations. No more recent studies assessing use of IAP in the UK were identified.

Another study found variation in the recommendations of local neonatal unit guidelines on the management of newborns at-risk of EOGBS, particularly offspring whose mothers had risk factors and were not treated with intrapartum prophylaxis.[48] The subsequent release of NICE draft guidance on the use of antibiotics for the prevention of early onset neonatal infection may reduce this variability.[46]

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's 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

2008 update report: *"There are a number of suggested screening strategies. None of these have been evaluated in randomised controlled trials."*

"Observational studies from the USA have suggested that the introduction of a national screening programme for antenatal GBS carriage has resulted in a substantial fall in the incidence of neonatal EOGBS sepsis from 1.5 per 1000 births to 0.5 per 1000 births from 1999 to 2000 and this fell further to 0.34 per 1000 births in 2003-2005."

No RCTs comparing screening for GBS in pregnancy versus no screening, or comparing different forms of screening for GBS were identified as being published since 2008.

Various countries including the US have implemented universal screening strategies. One systematic review was identified which compared universal swab based screening versus a risk based strategy or no intervention in observational studies.[50] We describe this review here, as well as additional studies describing the experience in the US as an example of a country that has instituted universal swab-based screening.

The systematic review included eight observational studies published between 1994 and 2006.[51-58] They all compared the rates of neonatal GBS sepsis in the different periods of time in which

the different strategies were used. The control periods in these studies always preceded the universal screening periods. The difficulty with interpreting the results of these studies is that factors other than the screening policy may differ between the time periods and influence the results.

The studies in the review were from the USA (four studies), Austria, Australia, Italy and Switzerland (one study from each of these four countries). Four studies were reported to compare universal swab-based screening versus no screening, and five to compare swab-based screening versus a risk-based approach (one study included both comparisons).

The review's meta-analysis found that overall, neonatal GBS sepsis was less common in periods where universal screening had taken place than in periods where no screening had taken place (OR 0.43, 95% CI 0.25 to 0.73). It also found that neonatal GBS sepsis was less common in periods where universal screening had taken place than in periods where risk based approaches were used (OR 0.25, 95% CI 0.16 to 0.37).

There are a number of limitations to this analysis. The main limitation is that factors other than screening could be contributing to the differences seen. As the groups being screened or not screened were not randomly allocated and were not contemporaneous, the groups could have differed in a number of factors other than screening strategy, including the proportion of women with risk factors. Ideally such studies should identify the risk factors of women giving birth in both periods and make sure these are similar in the periods being compared, and make adjustments for these factors in the analysis. The figures used in the review's analysis were unadjusted.

As with any meta-analysis, the validity of the results depends on how similar the studies being pooled were. Overall there was no statistical heterogeneity in the analyses, although there was in one sub-analysis. The lack of statistical heterogeneity does not mean that there was no clinical heterogeneity between the studies, for example in methods and population. The review did not seem to have considered in depth differences between the studies that may have influenced the validity of pooling them e.g. time of screening, method of screening, or method of detecting sepsis.

When data in the meta-analyses was checked against the original papers, a few discrepancies were identified. Firstly, data entered for the universal screening group in the study by Hafner et al[57] reports no sepsis cases in 3,952 births, while the paper itself reports 4 cases of GBS infections in this group. This study accounts for 21% of the weighting in the meta-analysis, the second largest weighting of any single study, so may have a considerable effect on the results.

The paper by Puopolo et al[52] referenced in the review does not include the figures for the risk-based screening control group included in the meta-analysis. These figures come from an earlier publication from the same research group, which is referenced in the Puopolo paper.[59] This earlier publication also includes figures for a no-screening period, it is not clear why data for this period was not included in the meta-analysis comparing universal screening versus no screening. A similar observation was made for the paper by Main et al.[58] This paper includes three different approaches (no screening, risk based approach, and universal screening approach), but only two are included in the review (universal screening, risk based approach). The figures included in the meta-analysis for the risk-based control group are actually from the no screening group, not from the risk-based screening group. It is not clear why these discrepancies exist, and it suggests that the results of the meta-analysis are not reliable.

The limitations in this meta-analysis mean that it is not possible to show that the differences in outcomes between groups are due to the method of screening, risk factor detection or other aspects of care.

From the update search we selected the most comprehensive US studies describing changes in GBS disease after the implementation of universal screening. These papers described data collected by the CDC as part of its Active Bacterial Core surveillance.

The largest US multistate study reported the trends in invasive GBS disease in the US between 1999 and 2005, and a subsequent article extended this reporting to 2006.[26,60] Figures for these and subsequent years are available from the CDC's Active Bacterial Core surveillance website.[61]

In the early 1990s in the US the incidence of EOGBS was about 1.7 per 1,000 livebirths.[1] At around this time the first statements from the American College of Obstetricians and Gynaecologists and the American Academy of Paediatrics about EOGBS prevention were made. The incidence of EOGBS began to decrease from around this time, and by around 1996-1997 the incidence of EOGBS was under 1.0 per 1,000 livebirths. At this point the US Centers for Disease Control and Prevention (CDC) and professional bodies in the US issued recommendations on the use of intrapartum prophylaxis for the prevention of neonatal GBS disease. These guidelines allowed the choice of either late antenatal bacteriological screening or a risk factor based strategy to guide selection of women to receive IAP.[60] After these guidelines were issued incidence of EOGBS continued to fall. By 2002 the incidence had fallen to below 0.5 per 1,000 livebirths, and at this point the CDC issued revised guidelines that advocated universal antenatal screening rather than risk based strategies for directing intrapartum antibiotic prophylaxis (IAP).

After 2002 the incidence of EOGBS fell by 27%, from 0.47 per 1,000 in the period 1999 to 2001 to 0.34 per 1,000 livebirths in the period 2003 to 2005.[26] This represented an absolute reduction of 1.3 EOGBS cases per 10,000 livebirths. However, after 2003 the rates began to increase, reaching about 0.40 per 1,000 livebirths in 2006 (p=0.03).[60] This increase was attributable to an increase in incidence of EOGBS in term black infants from 0.33 per 1,000 livebirths in 2003 to 0.70 cases per 1,000 livebirths in 2006 (p=0.002). Term white infants and preterm black or white infants did not show significant changes over this time.

The reason for this increase among term black infants is not clear. The same proportion of white and black mothers of term EOGBS cases had received screening (83%). Only a low proportion had received IAP (20% overall) between 2003 and 2006, although the proportion for whom IAP would have been indicated as a result of their antenatal screening results or other factors was not reported. The proportion of black mothers of cases receiving IAP was lower than that of white mothers of cases, but not significantly so (16% of black mothers vs. 23% of white mothers; p=0.09). Other factors that have been suggested to potentially have played a role include the higher GBS carriage rate among black women, the timing of screening, adequacy of specimen collection, laboratory processing, and implementation of adequate IAP.

Additional data collected by the ABC post-2006 was obtained from the CDC's website.[61] This data suggests that the overall rate of GBS fell after 2006, from 0.39 per 1,000 livebirths, to 0.26 per 1,000 in 2010 (provisional figures). When divided by race, the largest decline over this period was seen in black infants, falling from 0.92 per 1,000 in 2006 to 0.4 per 1,000 in 2010. Figures were not split by gestational age. These figures may not be comparable to those presented above as the publication describing figures for the period 1999-2005[26] excluded data from New Mexico, as this area was only added to the surveyed areas part way through the period being studied.

Limitations to this surveillance data were noted, including: that they cannot explain why differences in rates of GBS exist between the different ethnic groups, in part due to limited information about the cases being available; and that they may not be nationally representative as they only cover selected counties in the US. [62]

The main limitation to interpreting data from non-randomised studies is that multiple factors can be influencing the changes seen, and not just the introduction of screening. Other concerns raised have include the fact that these culture confirmed EOGBS figures may under-estimate the true incidence of GBS-related sepsis.[63] The concern is that use of antibiotics in labour may reduce the likelihood of obtaining a positive GBS culture, even if GBS is responsible for the infant's symptoms. This has led to the suggestion that the incidence of sepsis overall needs to be assessed, in addition to culture confirmed sepsis. One study on the rates of clinical sepsis in US between 1988 and 2006 has suggested that there has not been a change in GBS false-negative blood cultures since the introduction of IAP (see section on neonatal sepsis below for details).[64]

The authors of the paper responded to these criticisms by noting that clinical sepsis (rather than culture confirmed sepsis) is difficult to define, and it would not be feasible to implement collection of multi-state data based on complex definitions on a surveillance level.[65] As a result, they acknowledge that there was at that time (2008) no definitive data on the trends in culture negative GBS sepsis in the US since the guidelines were introduced. They do cite some other related figures that suggest that sepsis overall may also be decreasing. They say that the National Hospital Discharge Survey found that hospitalisations for sepsis in the first month of life have decreased by 23% from 1990 to 2002, with much of this decrease occurring after 1996 when the first CDC guidelines were issued. They also say that sepsis related early neonatal mortality (<7 days) dropped between 1985-1991 (24.9 per 100,000 livebirths) and 1995-1998 (15.6 per 100,000 livebirths), with average annual declines greater between 1995 and 1998 than between 1985 and 1991. Late neonatal mortality did not reduce in this period.

These figures have the same limitations as the other before and after figures, in that it is not possible to pinpoint the cause of these reductions. The figures quoted also do not cover the period since the recommendation of universal screening in 2002.

Even with universal screening in the US, there are still cases of EOGBS. One paper from the US looked at implementation of the guidelines and the characteristics of the EOGBS cases identified by CDC surveillance in 2003-2004, to investigate whether opportunities for EOGBS prevention were being missed, and how these remaining cases might be prevented.[39] It found that in 2003-2004, 85% of women had been screened for GBS before delivery, and 31.7% of women received intrapartum antibiotic prophylaxis. The incidence of EOGBS in this period was 0.32 per 1,000 livebirths.

The majority of the 254 infants with EOGBS (74.4%) were term infants. Among these term infants (61.4%) were born to mother who had screened negative for GBS antenatally. In cases where this was recorded (76.7%), the median gestational age of these women (35.6 weeks) at screening was similar to that for all term births (35.9 weeks), suggesting that this group did not just represent those who had antenatal screening too early.

On the basis of various assumptions about the test, including 96% specificity for colonisation status at labour, and assumptions about newborn colonisation rates without intrapartum antibiotic prophylaxis, and rates of EOGBS in colonised newborns, the study estimated that in the population covered, 44 to 86 cases of EOGBS might be expected among term infants whose mothers were negative for GBS colonisation antenatally. This was less than the 116 cases that

were actually seen in this group. The reasons for this discrepancy were not clear, although they suggest that screening more than 5 weeks before delivery, and problems with the collection of specimens, processing of cultures, and recording and reporting of screening results could be contributors. They noted that this discrepancy highlighted the need to further understand what contributes to these women not being picked up as GBS carriers in their antenatal screening.

Neonatal sepsis

One paper was identified which assessed the rates of clinical sepsis in neonates and young infants in the US between 1988 and 2006 based on hospital discharge diagnoses.[66] Data was obtained from the National Hospital Discharge Survey, an annual national probability sample of about 500 short-stay hospitals in the US. The analysis looked at discharges with ICD-9 codes 771.8 (infection in the perinatal period) or 038.0-038.9 (septicaemia) for hospital –born newborns, and infants admitted before age 3 months. It did not include infants with observation for suspected infection in the first 28 days of life (ICD V29.0). Infants not recorded as preterm were considered to be term. The periods compared were 1988-1995 (before IAP guidelines were issued), 1996-2001 (after initial IAP guidance was issued), and 2002-2006 (after CDC guidelines recommending universal screening were issued).

As well as looking at the rates of clinical sepsis as a whole in infants aged less than 3 months, the researchers looked at an early onset hospitalisation subgroup, as a proxy for early onset sepsis. This subgroup included term infants with sepsis diagnosed during delivery admission and discharged within ten days of birth. This definition would miss infants who were initially discharged and then re-admitted for sepsis, although the rapid onset of early onset sepsis may mean that this is unlikely to represent a large proportion of early onset cases. In addition it would miss any cases where early onset sepsis led to longer term hospitalisations. More importantly, this approach was not appropriate for use in preterm infants. This was because preterm infants often have prolonged admissions, and a discharge diagnosis of sepsis could have occurred at any point in this admission.

Between 1988 and 2006 there were 112,000 to 146,000 sepsis hospitalisations annually in infants aged less than 3 months, and a third were in preterm infants. The rate of hospitalisations in in 2006 was 30.8 per 1,000 births overall, with the rate three times higher in preterm than term infants (85.4 per 1,000 preterm births and 23.1 per 1,000 term births). Almost half of sepsis hospitalisations in term infants were early onset. There was no significant change in case fatality rate in this period (average 2.8%).

Over this period there were changes in gestational age, expected payment source, and pathogen identified among infants aged less than three months hospitalised for sepsis. The proportion of infants with sepsis who were preterm increased ($p<0.001$), as did the proportion for whom the expected payment source was Medicaid or other government source ($p<0.001$).

The proportion of cases for which a pathogen was identified remained stable over this period (12% on average). The authors suggesting that this meant that the use of IAP had not simply resulted in a reduction in the chances of GBS being detected, as if this was the case it might be expected to lead to a reduction in the proportion of sepsis cases where a pathogen was detected.

The proportion of cases where Streptococcus spp (not further specified) was identified reduced in this period (from 5.3% in 1988 to 1995 to 3.3% in 2002 to 2006; $p=0.043$). The proportion of cases where a Gram-negative bacteria was identified showed a non-significant increase in this period (from 3.1% in 1988 to 1995 to 4.9% in 2002 to 2006; $p=0.079$).

In terms of the 12% of cases with an identified pathogen, the majority were Streptococcus spp (38% of those with an identified pathogen), and 9% GBS. The next most commonly identified pathogens were Staphylococcus spp (26%), 23% *Escherichia coli*, and 8% other Gram negative bacteria.

The average annual rates of sepsis are displayed in Table 7 below. The rate of sepsis hospitalisations in term infants was significantly lower in 2002-2006 than in 1988-1995. The rate of early onset sepsis hospitalisation in term infants was significantly lower in both 1996-2001 and 2002-2006 than in 1988-1995.

Table 7: Average annual rate per 1,000 livebirths of sepsis hospitalisations in infants aged <3 months in the US

	1988-1995	**1996-2001**	**2002-2006**
Overall rate	34.7	33.5	29.5
Term births	27.8	24.8	21.8*
Early onset hospitalisation in term births	*14.3*	*11.4**	*10.3**
Preterm births	101.7	107.2	87.8
<28 weeks	*217.1*	*310.0*	*252.9*
28-36 weeks	*94.0*	*94.6*	*77.8*

*p<0.05 vs. 1988-1995 period

The paper also calculated the average annual percent change (AAPC) in rates of sepsis hospitalisation using regression methods (see Table 8 below). This analysis showed no significant trends in the change in overall sepsis hospitalisation rates or in early onset sepsis hospitalisation rates in term infants between 1988 and 2006. There was a significant trend for reduction in sepsis hospitalisation rates in term infants overall between 1996 and 2001, after introduction of the initial IAP guidance (AAPC -3.6%, 95% CI -5.0% to -2.0%), but no significant trend after this.

The analysis showed a significant trend for reduction in sepsis hospitalisation in preterm infants between 1988 and 2006 (AAPC -1.2%, 95% -2.2% to -0.1% over the entire period). There was a similar finding for preterm infants born at 28-36 weeks' gestation (AAPC -1.6%, 95% -2.7% to -0.5% over the entire period). However, there was a significant trend for increase in sepsis hospitalisation in preterm infants born at <28 weeks' gestation between 1988 and 1996 (AAPC +4.5%, 95% CI +2.1% to +6.9%), but no significant trends in subsequent periods.

Table 8: Average annual percent change (AAPC) in rates of sepsis hospitalisation in infants aged <3 months in the US

	1988-1995 (95% CI)	1996-2001 (95% CI)	2002-2006 (95% CI)
Overall rate	+0.2 (-0.6 to +1.0)	-3.6 (-7.2 to +0.1)	+2.2 (-1.3 to +5.8)
Term births	-2.3 (-7.6 to +3.3)	-3.6 (-5.1 to -2.0)*	+2.2 (-3.9 to +8.6)
Early onset hospitalisation in term births	*-1.0 (-6.0 to +4.3)*	*-7.1 (-16.2 to +3.0)*	*+2.4 (-1.1 to +5.9)*
Preterm births	-1.2 (-2.2 to -0.1)*	-1.2 (-2.2 to -0.1)*	-1.2 (-2.2 to -0.1)*
<28 weeks	*+4.5 (+2.1 to +6.9)**	*+1.1 (-1.7 to +3.9)*	*-5.4 (-11.7 to +1.4)*
28-36 weeks	*-1.6 (-2.7 to -0.5)**	*-1.6 (-2.7 to -0.5)**	*-1.6 (-2.7 to -0.5)**

*Statistically significant

Overall these results suggest that the bulk of the reduction in sepsis hospitalisation rates in term infants occurred after the introduction of general IAP guidance, and the rate then stabilised and did not change significantly after the recommendation for universal screening in 2002. Although this trend was not significant in the early onset sepsis hospitalisation subgroup, the pattern of changes was similar. Among the early onset sepsis hospitalisation subgroup the rate of hospitalisations became significantly lower in 1996-2001 than in 1988-1995, and remained lower in 2002-2006. Among preterm infants rates of clinical sepsis had already started to decrease in the 1988-1995 period, and the rate of decrease continued steadily to 2006.

These results are consistent with IAP having an effect on clinical sepsis rates. The authors also note that their findings are consistent with the findings of reduced EOGBS rates since widespread IAP, although the declines seen in clinical sepsis were smaller.

However, it is difficult to identify a specific impact of screening, as the initial IAP guidance suggested that either a risk factor approach or swab results could be used to guide IAP. There was no significant change in the rate of sepsis hospitalisation after the introduction of guidance recommending universal screening.

It is also the case that factors other than the IAP guidance could be influencing the results seen, and the decrease in clinical sepsis rates among pre-term infants even before the IAP guidelines does illustrate this point.

The authors suggest that preterm infants were “served somewhat less well by [the 2002] GBS prevention strategies”, citing data from a 2009 study showing lower adherence to IAP in preterm deliveries. They note that clinical sepsis rates are “an order of magnitude” higher than rates of culture proven sepsis from other studies. They also suggest that their finding of steady rates of recorded culture proven sepsis suggest no appreciable change in false-negative blood cultures. The figures on culture proven sepsis shown in the paper were for all sepsis hospitalisations in infants up to the age of three months, and therefore could include both early and late onset sepsis.

A second paper described the rates of invasive early-onset neonatal sepsis in the US between 2005 and 2008.[67] It was reported to be the first population-based estimate based on multistate data. It analysed data collected by the CDC's Active Bacterial Core surveillance (ABC) program and medical records. It included liveborn infants ≤2 days of age, >22 weeks' gestation, with bacteria isolated from either blood or cerebrospinal fluid. These figures would only include culture-proven sepsis, also they would only represent a subset of early onset sepsis, as it only covered the first two days of life rather than the usual six used to define early onset infections.

In the study period the rate of early onset culture-proven sepsis was 0.77 cases per 1,000 livebirths, and the rate remained stable over the period. There were 658 cases in all. The most common causes were GBS (37.8%), *E. coli* (24.2%), viridans *Streptococci* (17.9%), *Staphylococcus aureus* (4.0%), and *Haemophilus influenzae* (4%). Overall the case fatality rate was 10.9%, with the lowest case fatality rate for infants with viridans *Streptococci* (2.5%), and highest for infants with *E. coli* (24.5%).

Black preterm infants had the highest sepsis incidence (5.14 per 1,000) and case fatality (24.4%). Non-black term infants had the lowest sepsis incidence (0.40 per 1,000) and case fatality (1.6%).

Among preterm infants the most common infecting organism was *E. coli* (1.18 cases per 1,000 livebirths) and these infections had the highest case fatality rate (32.1%). Among term infants the most common infecting organism was GBS (0.22 cases per 1,000 livebirths); there were no deaths from GBS in term infants.

Of the *E. coli* with antimicrobial susceptibility results 66.9% were ampicillin resistant. One of the cases of *Staphylococcus aureus* was methicillin resistant (4.3% of those with susceptibility results recorded). Resistance of GBS isolates was not reported.

The study estimated that there were 3,320 culture-proven cases of early onset sepsis in the US annually between 2005 and 2008, and 390 deaths among these cases. GBS was the largest cause of culture-proven early onset sepsis (1,210 cases), but not the largest cause of deaths (90 deaths). *E. coli* was the next most common cause (840 cases) but was the largest cause of deaths (210 deaths).

The authors reported that their findings on pathogen distribution and disease incidence were similar to those from another multisite study of early onset sepsis between 2006 and 2009 in the US from the National Institute of Child Health and Human Development Neonatal Research Network (NRN). This NRN study estimated that there were an average of 3,310 cases of early onset sepsis annually, and 370 deaths. The NRN study also found that GBS was the most common cause among term infants, and *E. coli* the most common cause among preterm infants and also the most common cause of death.

The authors suggested that further reduction of GBS related early onset sepsis might require improved use of IAP in women with threatened preterm delivery, reduction of false negative GBS screens among women at term by better adherence to specimen collection and processing guidelines. They also say that "intrapartum prophylaxis based on universal GBS screening alone will not lead to elimination of early-onset GBS disease, and the US incidence is now close to the minimum that can likely to achieved under this strategy". They suggest that the existing burden of disease was likely to persist until other strategies such as GBS vaccination become available.

GBS meningitis

One paper analysed the rates of bacterial meningitis in the US between 1998 and 2007.[68] It found that the rates of GBS meningitis in children under two months of age did not change after

GBS screening of pregnant women was introduced in 2002 (65.2 cases per 100,000 population in 1998-2001; 62.5 cases per 100,000 in 2006-2007; difference -4%, 95% CI -10% to +2%). They say that most cases in 2002-2007 (86.5%) were late-onset so would not have been expected to be prevented by IAP. The percentage of cases before screening was introduced that were late onset was not reported.

EOGBS prevention in the UK

The Royal College of Obstetricians and Gynaecologists published a guideline on EOGBS prevention in 2003.[3] It recommended a risk factor based strategy rather than universal bacteriological screening. The figures published by the HPA only provide figures on EOGBS for a single year before this period (2000), making it difficult to look at the effect this may have had on EOGBS rates. The HPA reports that in England in 2000 the rate of EOGBS bacteraemia was 0.5 per 1,000; no figures were given for 2001 and 2002; in 2003 the rate in England and Wales combined was 0.35 per 1,000; in 2004 the rate in England was 0.32 per 1,000, and in 2005 it was 0.31 per 1,000. As described above, the figures have increased slightly between 2005 and 2010, but appear to remain below 0.5 per 1,000 (and at or below 0.4 per 1,000 in England). These cases only represent voluntarily reported culture-proven cases of EOGBS bacteraemia, and may not capture the entire burden of sepsis caused by GBS.

One small study in one hospital in the Republic of Ireland looked at the incidence of EOGBS before and after the RCOG guidelines.[10] It found that the incidence of EOGBS fell from 0.9 per 1,000 livebirths before the RCOG guidelines (1996 and 2002) to 0.45 per 1,000 livebirths between 2004 and 2009. However, as noted above, it is not possible to conclusively attribute such changes in incidence to one event such as the issuance of guidelines.

Antibiotic resistance

The CDC reports that resistance to clindamycin and erythromycin have increased over the past 20 years.[1]

In the study describing US EOGBS surveillance data for 1999 to 2005, all 4,882 isolates tested for susceptibility testing were reported to be susceptible to penicillin and ampicillin, although 0.2% were approaching the upper level of susceptibility for one or more of this family of antibiotics (beta lactams).[26] The US CDC 2010 GBS prevention guideline also notes that isolates with increasing minimum inhibitory concentrations (MICs) to penicillin or ampicillin have been reported in Japan and the US, but says that the clinical significance of these MIC values is unclear. One Japanese study has questioned the sensitivity and specificity of the methods used to identify reduced penicillin susceptibility in the Japanese isolates.[69] A more in depth assessment of this issue and of the broader literature about antibiotic resistance as it may relate to GBS prevention is outside of the scope of this update report, and may be an area that could benefit from additional review.

All of the isolates tested in the US surveillance study were susceptible to vancomycin, 32% resistant to erythromycin, and 15% resistant to clindamycin.[26] Almost all (99%) of those resistant to clindamycin were also resistant to erythromycin.

This level of erythromycin resistance (32%) reported in this US paper is higher than that reported by the HPA for England, Wales and Northern Ireland at around the same period (between 5% and 10% between 2002 and 2006).[6] Clindamycin resistance figures for the US (15%) were also slightly higher than for England, Wales and Northern Ireland (between 4% and 9% between 2002 and 2006).

The potential effect of IAP on antibiotic resistance in bacteria other than GBS also needs to be considered. The DH reports that antibiotic resistance is "one of the most significant threats to patient safety in Europe".[70] Therefore the potential benefits and harms of any programmes that could expand the need for antibiotics need to be considered carefully.

Due to the wide range of criteria, broad searches are carried out for literature relevant to the screening programme being assessed. However, these searches are of necessity targeted to the screening programme being assessed, in this case GBS screening. This means that wider literature not directly on GBS may not be identified. In particular, this may affect the areas of antibiotic resistance and potential harms of intrapartum antibiotics.

The search performed for this update was targeted towards evidence relating to screening for GBS in pregnancy and would not encompass the wider literature on antibiotic resistance. The evidence presented in this report should be interpreted in the wider context of the literature on antibiotic resistance. Another potential harm of IAP use raised in the previous update report was the long term effects on the infant. As the search for this update was targeted towards evidence relating to screening for GBS in pregnancy it is unlikely to have identified studies which looked at the effects of intrapartum antibiotic usage for reasons other than for GBS prevention.

A wider assessment of the literature relating to the potential impact of intrapartum antibiotic use on antibiotic resistance or long term effects on the infant could be considered as a possible area for further investigation.

Summary: Criterion 13 Not Met

There have been no RCTs assessing the effects of antenatal screening on mortality or morbidity from EOGBS. In the absence of RCTs it is difficult to quantify the potential impact of implementing screening for GBS in pregnancy.

Several countries have implemented universal antenatal screening without RCTs, including the US. A systematic review of observational studies found that universal screening reduced the risk of early neonatal sepsis compared with either no screening or a risk-based approach. However, as the groups in these studies are not randomised, or contemporaneous, it is difficult to determine to what extent changes are a direct result of the introduction of screening, as other differences in practice that occurred over the time periods compared may also have had an effect. In addition, there were discrepancies between the data in the meta-analysis and the data in the original studies that suggest that the meta-analytical results are not reliable.

The US was looked at in more depth as an example of a country which recommends universal screening. It has seen a considerable decrease in the incidence of EOGBS from about 1.7 livebirths per 1,000 to less than 0.5 per 1,000 livebirths since guidelines on IAP were introduced in the 1990s. Initially recommendations suggested that IAP could be guided by either universal antenatal bacteriological screening or a risk based strategy. Universal screening was recommended in 2002 in the US, but there was a significant increase in EOGBS between 2003 and 2006 (from 0.34 to 0.40 per 1,000 livebirths), attributed to increases among black term infants. The precise reason for this increase in this ethnic group is not known. Additional data collected by the CDC post-2006 suggests that the overall rate of GBS fell after 2006, from 0.39 per 1,000 livebirths, to 0.26 per 1,000 in 2010 (provisional figures). These more recent figures may not be comparable to the earlier figures, as they differ in the areas included.

There is also the suggestion that the changes may reflect a decreased likelihood of cultures being positive due to IAP use, with the culture negative cases of EOGBS sepsis being undetected

in these surveillance figures. One study from the US looked at the overall rates of neonatal sepsis based on hospital discharge diagnoses in infants up to the age of three months between 1988 and 2006.[64] It found a steady proportion of culture proven sepsis in this period, which they suggest indicated no appreciable change in false-negative blood cultures after the introduction of IAP. The overall rate of neonatal sepsis did not change significantly over this period, but the proportion of neonatal sepsis cases where Streptococcal bacteria were isolated reduced.

It is difficult to identify the specific impact of screening, as the reduction in sepsis in this study seen largely seems to have occurred after the introduction of the initial IAP guidance, which suggested that either a risk factor approach or swab results could be used to guide IAP.

14. 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

2008 update report: *"In the USA and in Australia and New Zealand the process of screening appears to be acceptable to health care providers. Indeed, a recent study in Canada reported that 92% of obstetricians and 79% of family physicians thought the benefits of universal screening outweighed the concerns. They also found that 24% of obstetricians and 30% of family physicians were theoretically willing to expose more than 10000 women to IAP to prevent a single neonatal GBS related death."*

"A recent small study suggested women with GBS colonisation identified by screening in Taiwan did not have a sustained increase in anxiety in the short term. This finding has been confirmed in the recent UK study of intrapartum screening. Anxiety levels were not affected by whether women had been found to be GBS carriers during pregnancy compared with those who had not been tested or who had been tested and found not to be carriers."

Summary: Criterion 14 Uncertain

The update search did not identify any studies looking at the acceptability of GBS screening to health professionals or the general public in the UK.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

2008 update report: *"As the real benefit of a screening programme can only be hypothesised from the available evidence it is not possible to explicitly weigh the benefit against the possible harm. There are, however, a number of major and direct possible harms from widespread use of IAP which merit further consideration. These include: i. Maternal anaphylaxis…. ii. Antibiotic resistance …..iii. Impact of antibiotic usage…. iv. Possible impact on neonatal sepsis….. v. Medicalisation of childbirth"*

The update search did not identify any RCTs of screening published since 2008.

Regarding the potential harms listed in the 2008 report, one study looking at US data from 2003 to 2004 from the CDC's Active Bacterial Core surveillance noted that there were no verified cases of anaphylaxis in a sample of about 7,600 women, 32% of whom had received intrapartum

antibiotic prophylaxis.[39] The CDC cite one case report of anaphylaxis with intrapartum antibiotic prophylaxis in the US published since 2008.[1,71] In this case an emergency Caesarean section was performed, and the mother and baby survived. However, the baby has significant neurological damage. The CDC report that estimates of the rate of anaphylaxis with penicillin vary between 4 per 10,000 and 4 per 100,000 recipients.[1]

One study from the US found that one woman had symptoms indicative of an allergic reaction (itchy throat, difficulty breathing, swollen lips) after receiving gentamicin as IAP.[22] This was equivalent to 0.2 per 1,000 deliveries (based on the figures presented in the paper this was roughly 0.6 per 1,000 women treated with antibiotics).

The issue of antibiotic resistance is discussed in Criterion 13.

One paper from the US raised the issue of potential unintended effects of the 2002 CDC GBS prevention guidelines.[72] At least four hours of IAP before delivery is the recommended as the optimal duration for prevention of GBS.[1] The study assessed whether clinicians were changing their management to achieve this duration of IAP in GBS positive women, even though the CDC guideline did not recommend that this should be done.

The study found that more than three quarters of clinicians (78.6%) reported changing their management strategies in some way in GBS positive pregnancies in multiparous women. This included asking GBS positive women to come into hospital at the first signs of labour (35.7%), or admitting them to hospital before they were in active labour (11.4%) or earlier in the course of labour than they would do otherwise (57.1%).

More than three quarters of clinicians (77.1%) reported changing their labour management strategies in GBS positive pregnancies. This included delaying pushing (21.4%), turning off or decreasing oxytocin infusion (27.1%), or delaying or avoiding artificial rupture of membranes (74.3%).

Just over a third of clinicians (35.7%) felt that trying to achieve this 4 hours of IAP caused them additional stress or anxiety, and 42.9% felt it caused additional stress or anxiety to the delivery floor staff. Over half (54.3%) felt it caused additional stress or anxiety to the patient and 30% felt is caused additional stress or anxiety to the patient's family.

The authors note that the effects of these changes in management on the mother and the neonate are not known, and may not be in the best interest of either. CDC's revised 2010 guidelines suggest that there is not sufficient data to make recommendations about the timing of procedures intended to facilitate progression of labour, such as amniotomy, in GBS-colonised women.[1] They say that if possible procedures should be timed to allow the delivery of at least four hours of IAP before delivery. However, they state that no medically necessary obstetric procedure should be delayed in order to achieve four hours of GBS prophylaxis before delivery.

Summary: Criterion 15 Uncertain

The benefits and harms of screening remain difficult to balance. This is in part due to the fact that the benefits and harms of screening remain unquantified by RCT evidence. EOGBS bacteraemia in the UK is relatively uncommon, occurring in about 0.41 per 1,000 livebirths in the UK, and deaths from EOGBS may be about 0.04 per 1,000 livebirths. These figures come from voluntary reporting of culture-proven GBS bacteraemia, and therefore may not represent all cases of GBS bacteraemia. The figures also only apply to livebirths, therefore do not include stillbirths where GBS is present.

As about 21% of women in the UK are estimated to be colonised by GBS antenatally, this suggests that if a universal screening strategy was implemented then intrapartum antibiotics would be required in about 210 women per 1,000 pregnancies.

The harms in terms of anaphylaxis are likely to be rare, but are serious. In addition, the potential for increasing antibiotic resistance is a harm on the population level, and this is difficult to quantify and weigh up against individual-level benefits.

The potential harms from intrapartum antibiotics will also apply to women detected through risk-based strategies. A recent UK HTA found that about 22% of women had at least one risk factor, therefore if IAP were given to every woman with a risk factor, a similar number would be expected to be treated with IAP as would be expected if they had been screened.

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

2008 update report: *"A recent HTA funded study to assess the cost-effectiveness of screening strategies for GBS using observational data has made a number of important observations. Although the model was based on data which have been more recently updated, some of the observations remain pertinent. When considering a wide range of potential screening strategies, several strategies are cost-effective at accepted levels of willingness-to-pay thresholds currently used by NICE. However, as with all cost-effectiveness models, there are aspects to screening for GBS which are not easy to incorporate in the model such as the effect of widespread use of antibiotics on the development of antibiotic resistance and the impact this will have; the impact of increased medicalisation of birth on maternal and neonatal outcomes; and the effect of very rare but potentially catastrophic anaphylaxis in labour."*

The update search identified two cost effectiveness studies published since 2008.[73,74] One study describing the economic costs of GBS disease in infants in England was also identified.[75]

One of the cost-effectiveness studies[73] was a publication of the 2008 UK HTA[17], the results of which are described in the previous NSC update report (see italicised text above). It examined ten alternative strategies for directing IAP:

1. Routine untargeted IAP to all (treat all)
2. No screening and no antibiotic prophylaxis (do nothing)
3. Microbiological culture of vaginal and rectal swabs taken at 35–37 weeks of gestation
4. Rapid testing during labour using the PCR
5. Rapid testing during labour using the OIA
6. Screening using one or more of five risk factors (previous baby affected by GBS; GBS bacteriuria detected during the current pregnancy; preterm labour; prolonged rupture of the membranes; and fever in labour)

7. Risk factors and PCR: women who possess one or more of the five risk factors are further tested for GBS using the PCR test and only treated if the test result is positive
8. No risk factors and PCR: women who possess one or more of the five risk factors are treated with antibiotics but those who do not exhibit any of the risk factors have a PCR test and treated if the result of this test is positive
9. Risk factors and OIA: women who possess one or more of the five risk factors are further tested for GBS using the OIA test and only treated if the test result is positive
10. No risk factors and OIA: women who possess one or more of the five risk factors are treated with antibiotics but those who do not exhibit any of the risk factors receive OIA test and treated if the result of this test is positive

Briefly, it found that the "do nothing" strategy was the least costly but least effective, costing £1,059 per woman on average and with 36 infants per million dying from EOGBS. Routine IAP (without screening) was the most cost effective strategy, with an incremental cost effectiveness ratio (ICER) of £32,000 per case of EOGBS avoided, and £427,000 per EOGBS death avoided compared with doing nothing (no screening and no IAP). The authors equated this to £15,815 per QALY by assuming that all babies who avoided death from EOGBS would survive in full health. The authors noted that given wider concerns about routine antibiotic use (e.g. the potential for increasing antibiotic resistance) routine IAP was unlikely to be acceptable.

Excluding the routine IAP strategy, it found that the ICER for risk based screening compared with doing nothing was £50,000 per case of EOGBS avoided, and £660,000 per EOGBS death avoided. The ICER for antenatal culture based screening compared with doing nothing was £45,000 per case of EOGBS avoided, and £633,000 per EOGBS death avoided. The authors equated this to £23,444 per QALY for culture based screening. Rapid testing by PCR or OIA were found not to be cost effective.

Sensitivity analysis showed that the analysis was sensitive to the cost of the culture test. An increase in the cost of the test from £10.63 to £11.50 made a risk factor based approach more cost effective. If the assumption that all women who deliver before the culture based screening test at 35–37 weeks are treated with IAP was removed, risk based screening again became more cost effective than culture-based screening. The cost of PCR had to be reduced from £29.95 to £7.00 before it became the most cost effective strategy.

The other cost-effectiveness analysis looked only at the subset of women with GBS colonisation in a previous pregnancy, and assessed whether it was more cost effective to just treat all these women with IAP, rather than re-screening and treating based on the results.[74] It found that routine IAP without screening was more cost effective than screening. The model did take into account the possibility of maternal death from antibiotic anaphylaxis, but did not consider the effects on outcomes such as antibiotic resistance. This analysis was based on a US setting, and is not directly relevant to the UK, where screening is not currently offered.

The third study identified looked at the extra economic costs incurred in the first two years of life by infants who had GBS disease during the first 90 days of their life in England.[75] It calculated these costs based on the health and social resource usage of 138 infants with GBS disease in England and 305 control infants without the disease matched for time of birth and birth weight. Of the infants with GBS, 102 had early onset GBS, and 36 had late onset GBS disease. The GBS infants were identified through the HPA or London Respiratory and Systemic Infection Laboratory, or though microbiologist or paediatrician referral between February 2000 and

February 2003. Control infants had to have no clinical signs of sepsis in the first six days of life. Health and social care costs were extracted from hospital notes, parental questionnaires when the child was aged one and two years, and GP and health visitor questionnaires when the child was two years old. Costs were expressed as pounds and valued at 2003 prices.

The study found that infants with GBS had: longer stays in high dependency care, and more consultations with community midwives, community paediatricians, social workers, portage co-ordinators, physiotherapists, and speech and language therapists (all p≤0.001). Use of other health and social care resources was not altered.

Overall, the average health and social care cost in the first two years of life in infants with EOGBS was £9,273.50, in infants with LOGBS it was £20,907.40, and for infants without GBS it was £6,260.70. The largest contributor to the costs in infants with GBS was the cost of initial hospital care. The costs for infants with EOGBS is significantly higher than those without GBS (difference £3,012.80; p=0.03). The costs for infants with LOGBS is also significantly higher than those without GBS (difference £14,646.70; p≤0.001). Based on the costs calculated, and the number of GBS cases reported to the HPA in 2001 (568 cases), they estimated that the additional cost to the UK of infants with EOGBS and LOGBS is about £1.6 million per year. Using the same strategy as used in this study, the costs specifically associated with EOGBS (377 cases in 2001)[4] would be estimated as about £568,000 per annum.

Regression modelling which took into account GBS status and confounding variables found that the increase in costs attributable to EOGBS was £4,767.13, and the increase in costs attributable to LOGBS was £10,323.45. In the regression analyses prematurity was noted to be a significant cost driver, and the study reported that there was little difference in the cost of GBS compared with no GBS when only term infants were included in a separate regression analysis. No figures were shown for this analysis. The authors suggest that these findings suggest that the needs of premature infants with GBS should be specifically addressed. They note that intrapartum prophylaxis will not impact prematurity associated with GBS, but that vaccination may reduce prematurity associated with GBS as well as reducing GBS infection in infants.

The authors note that their study does not address potential longer term costs of GBS disease, after the first two years of life. They also note that cost data alone cannot determine the most efficient allocation of finite resources, and that this requires economic modelling. They say that the UK HTA cost effectiveness model did not have access to costs estimated from formal studies such as this. They suggest that their estimated costs could be used to inform such cost-effectiveness models.

Summary: Criterion 16 Not Met

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

17. All other options for managing the condition should have been considered (eg. improving treatment, providing other services), to ensure that no more

cost effective intervention could be introduced or current interventions increased within the resources available

2008 update report: *"Other options have been considered: (a) antenatal treatment of mothers identified as being carriers does not reduce the likelihood of GBS colonisation at the time of delivery (b) management of neonates after delivery. Many neonates with EOGBS disease have symptoms at or soon after birth and as neonatal sepsis can progress rapidly to death, whether their mothers have received intrapartum antibiotics or not, any newborn infant with clinical signs compatible with infection is treated promptly with broad spectrum antibiotics which provide cover against GBS and other common pathogens. Taking skin or blood cultures at birth from babies born to women who carry GBS will not be helpful as these take from between 24 and 48 hours to return, during which time almost all of the babies who will develop EOGBS neonatal sepsis will be ill."*

The update search identified RCTs of oral antenatal antibiotics and of vaginal cleansing with chlorhexidine (see Criterion 10). The results of these studies support that these approaches are not useful in the prevention of EOGBS.

The literature identified also supported the rapid onset of EOGBS disease (see Criterion 2). Rapid real time PCR could be considered as an alternative to culture based methods of testing samples from newborns for GBS, as these could speed up identification of colonised or infected infants. Studies would need to be performed first to assess the performance of these tests in this setting. In the absence of routine maternal GBS screening in pregnancy, this would need to be carried out in all infants, and the cost may be prohibitive.

A risk factor based strategy is the option currently used in the UK for prevention of EOGBS. Criteria 11 and 12 addresses local and national UK guidance regarding this strategy, and whether current clinical management has been optimised. The evidence discussed in these criteria suggest that clinical management based on risk based assessment may not yet be optimised. Previous cost-effectiveness analyses has suggested similar incremental cost effectiveness for a risk based approach and universal screening (see Criterion 16 for details).

Summary: Criterion 17 Not Met

The studies identified by the update search supported that oral antenatal antibiotics and vaginal cleansing with chlorhexidine are not useful in the prevention of EOGBS. It also supported that screening of neonates for GBS to identify those at risk of EOGBS is not currently feasible.

Optimisation of clinical management based on risk factor based screening may be an alternative option for consideration.

18. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

2008 update report: *"In the absence of national screening in the UK, no quality assurance standards have been agreed. The Health Protection Agency have produced a Standard Operating Procedure for the handling of GBS culture specimens in the laboratory."*

This remains unchanged. The update search identified one publication reporting a survey of microbiological procedures for GBS screening, diagnosis and serotyping, as well as an initial external quality assessment of GBS serotyping.[25] The publication was part of the Europe-wide DEVANI (DEsign of a VAccine against Neonatal Infections) program, which aims to better understand GBS epidemiology in Europe to aid vaccine design.

This paper highlighted variations in practices across Europe, and also reported that standardised methods for serotyping and molecular typing of GBS strains had been agreed within the participating centres.

Summary: Criterion 18 Not Met

There are UK standard operating procedures for detecting GBS in vaginal and rectal swabs. However, there are no plans or standards relating to managing or monitoring universal antenatal screening as it is not currently recommended in the UK.

19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

2008 update report: *"If the strategy of offering all women swab-based screening at 35-37 weeks was adopted, one or two swabs from every women during pregnancy will place an additional burden on the maternity and laboratory services. An average sized maternity unit will provide care for approximately 3000 to 3500 women a year.*

The majority of maternity care providers will see women between 35 and 37 weeks for routine care, however, in many units this visit will take place either at the GP surgery or at the woman's home. Transportation and processing of swabs will require additional microbiology laboratory time.

In addition, approximately 25% of these women (750 women per unit) will require IAP with the costs of intravenous access, antibiotics and staff workload. The provision of adequate initial and on-going training of staff will also require investment."

Summary: Criterion 19 Not Met

The issues raised in the 2008 report still apply. In addition, if new molecular tests were used in an intrapartum setting this would also carry resource implications. It would need appropriate equipment for testing, staff training, and staff time to provide the tests. There would also need to be the ability to test women around the clock.

20. 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

Criterion 20 Not Assessed

21. 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

Criterion 21 Not Assessed

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members

Criterion 22 Not Applicable

Implications for policy

The evidence published since 2008 has not substantially changed the evidence base regarding GBS screening, and therefore does not support a change in policy.

Implications for research

The recommendations for future research remain similar to those from the previous update report. This includes:

- Ideally an RCT to assess the effects of universal antenatal screening. However, due to the large numbers of women that would be required in order to identify the effect of screening, such an RCT may not be feasible.
- Studies looking at the long term effects of intrapartum antibiotic prophylaxis on the offspring, including review of existing evidence from all indications
- Research aimed at developing a GBS vaccine and considering how best such a vaccine could be utilised and whether it could be cost effective
- Further research to assess the performance and feasibility of rapid PCR based methods for detecting GBS in the labour ward in a UK setting
- Updated cost effectiveness analyses including new bedside testing rapid PCR systems for GBS in the labour ward, and estimated additional costs of EOGBS in the first two years of life
- An updated study to actively monitor of the incidence and causes of neonatal sepsis in the UK, ideally supported by mandatory reporting of EOGBS. Such research could also assess trends in antibiotic resistance, use of intrapartum antibiotic prophylaxis, and incidence of anaphylaxis

Additional areas that could be considered based on the uncertainties identified in this report include:

- Studies assessing concerns about antibiotic resistance from widespread IAP use
- Research into the factors that influence vertical transmission of GBS and development of EOGBS in the offspring
- Research into the effectiveness of the current risk based strategy in reducing rates of EOGBS and death
- Research to assess uptake of the recommendations from the NICE antibiotics for early onset neonatal infection guidance and revised RCOG guidelines once finalised, as well as qualitative research into facilitators and barriers to implementation

Methodology

Search strategy

Background:
The previous literature search on this topic for the National Screening Committee was undertaken in April 2008. An update search for this report was carried out in October 2011.

Sources searched: Medline, Embase, Cochrane Library.

Dates of search: Medline 2008-October Week 3 2011; Embase 2008-2011 Week 43, Cochrane Library 2011 Issue 10 and 4.

Search strategy:
Medline (OVID interface)

1 (group b adj streptococc*).tw.
2 streptococc* agalactiae.tw.
3 exp streptococcus agalactiae/
4 1 or 2 or 3
5 screen$3.tw.
6 (test or tests or testing).tw.
7 detect$.tw.
8 exp mass screening/
9 exp prenatal diagnosis/
10 exp risk factors/
11 (bacteriological or microbiological).tw.
12 swab$.tw.
13 culture$.tw.
14 (colonisation or colonization).tw.
15 marker$.tw.
16 exp biological markers/
17 membrane rupture$.tw.
18 (preterm labour or pre-term labour or preterm labor or pre-term labor).tw.
19 maternal fever.tw.
20 (risk based or risk-based).tw.
21 or/5-20
22 4 and 21
23 (2011* or 2010* or 2009* or 2008*).ed.
24 22 and 23
25 (200801* or 200802*).ed.
26 24 not 25

Embase (OVID interface)

1 (group b adj streptococc*).tw.
2 streptococc* agalactiae.tw.
3 exp streptococcus agalactiae/
4 1 or 2 or 3

5 screen$3.tw.
6 (test or tests or testing).tw.
7 detect$.tw.
8 exp mass screening/
9 exp prenatal diagnosis/
10 exp risk factors/
11 (bacteriological or microbiological).tw.
12 swab$.tw.
13 culture$.tw.
14 (colonisation or colonization).tw.
15 marker$.tw.
16 exp biological markers/
17 membrane rupture$.tw.
18 (preterm labour or pre-term labour or preterm labor or pre-term labor).tw.
19 maternal fever.tw.
20 (risk based or risk-based).tw.
21 or/5-20
22 4 and 21
23 (2011* or 2010* or 2009* or 2008*).em.
24 22 and 23
25 limit 24 to embase

Cochrane Library (Wiley Online Library interface)
#1 (group b near/5 streptococc*):ti or (group b near/5 streptococc*):ab
#2 (streptococc* agalactiae):ti,ab
#3 MeSH descriptor Streptococcus agalactiae explode all trees
#4 (#1 OR #2 OR #3)
#5 screen*:ti,ab
#6 (test or tests or testing):ti,ab
#7 detect*:ti,ab
#8 MeSH descriptor Mass Screening explode all trees
#9 MeSH descriptor Prenatal Diagnosis explode all trees
#10 MeSH descriptor Risk Factors explode all trees
#11 (bacteriological or microbiological):ti,ab
#12 swab*:ti,ab
#13 culture*:ti,ab
#14 (colonisation or colonization):ti,ab
#15 marker*:ti,ab
#16 MeSH descriptor Biological Markers explode all trees
#17 membrane rupture*:ti,ab
#18 (preterm or pre-term) next (labour or labor):ti,ab
#19 maternal fever:ti,ab
#20 risk based:ti,ab
#21 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)
#22 (#4 AND #21), from 2006 to 2011

Results

All results were downloaded into a spreadsheet and 349 duplicates removed.
A total of 1035 citations remained.

Database	No. citations retrieved	Exclusive
Medline	486	466
Embase	870	553
Cochrane Library	28	16
Total	**1384**	**1035**

In addition, 6 editorials, 20 non-systematic reviews, 13 articles included in previous searches and 9 articles commenting on other papers were removed.

The title and abstracts of the remaining citations, and where necessary and available the full text, were examined for relevance to group B streptococcus antenatal screening. After this 302 citations remained, and have been classified as follows:

Category	No. of citations
Systematic reviews	4
Guidelines	7
Guideline adherence	12
Health Technology Assessment	1
Incidence – maternal & neonatal	13
Incidence – maternal	38
Incidence – neonatal	32
Transmission	5
Prevention	3
Prevention – screening, tests	105
Prevention – screening programme	25
Prevention – antibiotic prophylaxis	33
Prevention – risk factors	11
Prevention – vaccines	12
Audit	1
Total	**302**

Additional references and top-up search: The charity Group B Strep Support (GBSS) provided a list of about 90 references published since 2008, some of which were published after the original search date for this update (October 2011) and therefore would not have been identified in the original update search. To ensure consistency of approach across the literature, a top-up search was undertaken to identify relevant literature published between October 2011 and February 2012. This search covered the same sources as the original update search, and its results overlapped with the references sent by GBSS.

Dates of search: Medline October 2011-February Week 4 2012; Embase 2011 Week 44-2012 Week 8, Cochrane Library 2012 Issue 2 (CDSR and Central) and 1 (Other components).

Search strategy.

Medline (OVID interface). Similar strategies were used in Embase and the Cochrane Library

1 (group b adj5 streptococc*).tw.
2 streptococc* agalactiae.tw.
3 exp streptococcus agalactiae/
4 1 or 2 or 3
5 screen$3.tw.
6 (test or tests or testing).tw.
7 detect$.tw.
8 exp mass screening/
9 exp prenatal diagnosis/
10 exp risk factors/
11 (bacteriological or microbiological).tw.
12 swab$.tw.
13 culture$.tw.
14 (colonisation or colonization).tw.
15 marker$.tw.
16 exp biological markers/
17 membrane rupture$.tw.
18 (preterm labour or pre-term labour or preterm labor or pre-term labor).tw.
19 maternal fever.tw.
20 (risk based or risk-based).tw.
21 or/5-20
22 4 and 21
23 (2011* or 2012*).ed.
24 22 and 23
25 20110*.ed.
26 24 not 25

Top-up search results

All results were downloaded into a spreadsheet and 15 duplicates removed.
A total of 156 citations remained.

Database	No. citations retrieved	Exclusive
Medline	59	59
Embase	110	96
Cochrane Library	2	1
Total	**171**	**156**

In addition, 1 editorial, and 14 articles included in previous searches were removed. The title and abstracts of the remaining citations, and where necessary and available the full text, were examined for relevance to group B streptococcus antenatal screening. After this 46 citations remained, and have been classified as follows:

Category	No. of citations
Systematic reviews	1
Non-systematic reviews	2
Guideline adherence	5
Incidence – maternal & neonatal	2
Incidence – maternal	5
Incidence – neonatal	4
Transmission	2
Prevention – screening, tests	11
Prevention – screening programme	1
Prevention – antibiotic prophylaxis	6
Prevention – risk factors	6
Prevention – vaccines	1
Total	**46**

Quality

Update reports aim to provide a narrative overview of the best quality and informative studies relevant to the 22 NSC criteria for screening programmes published since the previous NSC review of the screening policy in question. They are not systematic reviews, but use systematic searches to identify relevant evidence and apply a systematic approach to study inclusion. Due to the large amount of literature that is usually identified as potentially relevant to the 22 multi-faceted criteria, pragmatic decisions are made about the focus of the reports and study inclusion. The NSC identifies key areas of uncertainty raised in the previous policy review, and these are targeted in the update report, along with other areas where the evidence has advanced significantly. Key aspects of this approach are summarised here.

The details of the 348 relevant papers identified in the systematic searches and the additional post-2008 papers highlighted by GBSS were provided to Bazian. A first pass appraisal at abstract level was carried out by a single reviewer, followed by a retrieval of selected full text papers. Full texts were also assessed by a single reviewer, who identified the best quality and most relevant studies for inclusion. The report focuses on addressing key areas of uncertainty identified in the previous report. Relevant guidelines, systematic reviews and RCTs addressing these issues were included. Other types of evidence are considered for inclusion for Criteria where this type of study design is appropriate (e.g. where looking at prevalence and incidence of conditions, or their natural history). Where appropriate (e.g. for criteria looking at incidence/prevalence or current practice), studies from the UK are prioritised for inclusion as they are most relevant to screening decisions being made in a UK context.

The NSC also requested that Bazian include UK Health Protection Agency data on the rates of early onset GBS bacteraemia. Additional relevant studies that were identified in the process of preparing the report were also included e.g. studies cited by other studies. We excluded conference abstracts and non-English language studies.

Specific approaches to inclusion and exclusion used within key criteria are described in more detail below.

In Criterion 5 we focused on the two main questions relating to the testing: (1) how well does antenatal screening as currently performed predict of GBS colonisation at the time of labour; and (2) do rapid intrapartum tests perform well compared to intrapartum culture?

For the first question we included studies that used compared the results of antenatal and intrapartum GBS tests using culture methods broadly in line with those recommended by the US CDC and UK HPA, i.e. selective broth culture followed by subculture.

We did not assess studies looking at different detection methods (e.g. different swab sites, swab transport media, or culture broths or agars) performed at the same point in time. We also did not assess studies looking at the effect of different pre-swabbing practices on detection (e.g. pelvic exam). We did not include studies in these areas as there are recommended methods for swabbing and culture testing e.g. from the UK HPA and US CDC. We felt it was more appropriate to focus on the performance of these accepted methods rather than comparisons versus other non-accepted methods. The rationale being that if better methods had been identified, they would have been adopted by e.g. the CDC in their 2010 guidance.

For the second question we only included studies using rapid tests on swabs collected intrapartum, as this is how the test would ideally be used. We did not include studies of rapid tests performed only on antenatal swabs, unless the study included an intrapartum culture reference standard for comparison. Again, we only included studies that used an intrapartum culture method broadly in line with those recommended by the US CDC and UK HPA, i.e. selective broth culture followed by subculture. We excluded studies that used direct plating of swabs as the reference standard method of detection.

In addition, in order to be of use for intrapartum screening, the test needs to be carried out directly on material collected on the swabs, without the need for enrichment by culture, as this step adds to the time taken to obtain the results and begin treatment. Therefore we only included studies that have assessed rapid tests using non-enriched samples for intrapartum testing.

We focused on real time PCR tests and optical immunoassay tests, as these were found to be the most accurate and rapid tests in a UK HTA.[17] Studies solely looking at the ability of new test to serotype GBS were excluded, as the ability to serotype GBS is not currently a key part of existing screening programmes, and serotype does not currently influence treatment. We also excluded studies assessing the performance of rapid tests using GBS or other bacterial isolates rather than clinical samples, as the performance of the tests on clinical samples will be most informative about its potential performance in a real world screening programme.

If antenatal real time PCR tests perform better that antenatal culture in predicting intrapartum GBS colonisation, then they may have a role at this stage. We therefore would have included studies which assessed the performance of antenatal real time PCR tests against intrapartum culture. The update search identified no studies that carried out such an assessment.

In Criterion 13 due to the lack of RCT evidence on the effects of screening we looked at evidence about the rates of EOGBS before and after universal screening in the US as a country which has introduced universal screening. We focused on the studies describing multi-state CDC Active Bacterial Core surveillance data, as this covered the largest number of women.

Data in the final report were checked against the original papers for accuracy by a second reviewer. The report was also checked for clinical sense.

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