Universal antenatal screening for group B *Streptococcus* (GBS) may do more harm than good

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Stand-first:

There are regular calls to introduce routine screening for group B *Streptococcus* colonisation in late pregnancy in the UK. In this paper, Seedat and colleagues argue that screening should not be introduced at present because of the potential harm from high levels of unnecessary treatment with antibiotic prophylaxis and the uncertainty of screening effectiveness.

Group B *Streptococcus* (*Streptococcus agalactiae,* GBS) is the commonest cause of neonatal sepsis and meningitis in many developed countries.[1] In the UK, GBS causes invasive disease in the first six days of life (early onset GBS or EOGBS) in around 1 of every 2,000 live births.[2] [3] To prevent EOGBS, intrapartum antibiotic prophylaxis (IAP), usually intravenous penicillin, is the recommended mainstay internationally. In the UK, a risk-based strategy is recommended, whereby pregnant women presenting with GBS risk factors are offered IAP during labour.[4-7]

There are regular media and political calls to introduce universal antenatal GBS screening as an alternative means of selecting women for IAP. Advocates point to countries across Europe and North America where screening is recommended[8-22] and where EOGBS reductions have been observed.[23-25] However, when examining the evidence using established screening criteria,[26] it becomes clear that the effectiveness of screening is uncertain and that screening has potential harms. Here, we explain the evidence-based reasons not to introduce universal screening in the UK based on UK National Screening Committee (UK NSC) evidence reviews and key papers published since,[27] [28] namely high levels of overtreatment, unknown potential hazards from screening and treatment with IAP, and uncertain benefit.

Background

GBS is a Gram-positive bacterium that colonises the gastrointestinal and genitourinary tract in approximately 20% of pregnant women.[29-31] It usually causes no harm.[9] However, if a woman is colonised at the time of labour, around 36% will transmit GBS to their neonate.[32] Crucially, the majority of neonates colonised with GBS will remain asymptomatic; however, about 3% will develop EOGBS disease.[32] Neonates with EOGBS present with sepsis in 63% of cases, pneumonia in 24%, meningitis in 13%,[3] and around 5% to 10% die as a result.[2] [3] [33] Neurological impairment is reported in up to 15.8% of EOGBS survivors,[34-36] though long-term outcomes are not well researched. The true burden of EOGBS is likely higher as most of the research only describes culture-confirmed cases while the infecting organism in approximately half of neonatal sepsis cases cannot be isolated.[37] EOGBS is an important health condition causing considerable morbidity and mortality.

A risk-based strategy to prevent EOGBS has been recommended in the UK since 2003.[4-7] Pregnant women presenting with GBS risk factors of preterm labour, GBS colonisation, a previous infant with GBS disease, GBS bacteriuria, intrapartum fever, and chorioamnionitis are offered IAP.[4-7] However, 65% of neonates with EOGBS do not have risk factors and are therefore not eligible for IAP.[3]

Universal screening for GBS

Universal screening involves the collection of specimens using rectovaginal swabs at 35 to 37 weeks gestation, which are processed using selective culture media, to identify women colonised with GBS so that IAP can be offered to those testing positive.[38] Therefore, screening would be offered to all term pregnant women and could detect some of the 65% of EOGBS cases without risk factors.

Screening was first introduced in the US where the incidence of culture-confirmed EOGBS was around 1.7 per 1,000 live births. The incidence reduced to 0.4 in 2001 following the 1996 recommendation that either a risk-based or screening strategy could be implemented. This reduced again to 0.3 in 2004 after the recommendation that screening should be implemented in 2002.[24 25] Screening has continued since and incidence has most recently been reported to be 0.22 per 1000 live births.[39] Most countries recommending screening have similarly seen a reduction or stabilisation in the incidence of EOGBS,[23 40] though some have not.[41] In the UK and Republic of Ireland, with no screening but risk based prevention, the incidence was much lower than the US before screening, at 0.57 per 1,000 live births (n=518 in 2014–15). However, there was a statistically significant increase from 0.48 in 2000–01, before national guidelines were published,[2 3] the reasons for which are unclear.

Overdiagnosis and potential harm

As identified above, only a small percentage of neonates born to women colonised with GBS will develop EOGBS. Therefore, the proposed screening programme would detect a large number of women who carry GBS and would be eligible for IAP when, if left untreated, their baby would not have developed EOGBS. Based on UK data, antenatal culture would correctly predict which babies develop EOGBS in around 2/1,000 (0.2%) pregnant women

(see figure 1, 205/126,159 in 2000–01 and 350/138,933 in 2014–15). This positive predictive value of the test of 0.2% is orders of magnitude worse than in other national screening programmes, and so would deliver an unacceptably high level of false positive results. A cost-effectiveness model published in 2007 also estimated that adding screening to risk-based prevention would result in 99.8% overtreatment (increasing antibiotic use in pregnancy from 11% to 27%).[42] Similarly, an Australian centre reported 1,191 women would need to be treated with IAP to prevent one case of EOGBS.[43] Although the model contains some limitations because of evidence gaps, the estimates support the high levels of overtreatment that would occur when introducing screening.

As 99.8% of pregnant women and their babies would be overtreated, an examination of potential harms is particularly important for GBS screening. A systematic review of 30 studies found little evidence to quantify the potential harms of IAP to mothers and babies.[44] Although a range of adverse effects were investigated, studies specifically on GBS prophylaxis were observational and at risk of bias while 13 RCTs at lower risk of bias investigated antibiotics and regimens different to GBS prophylaxis. Key findings from the review were around changes in gut microbiota, long term functional impairment, and antibiotic resistance.

There was consistent observational evidence that IAP for GBS prophylaxis alters neonatal gut microbiota.[45-52] Gut microbiota changes have been associated with metabolic problems such as obesity and diabetes, atopic, inflammatory, and autoimmune problems such as asthma and necrotising enterocolitis, and autism.[53-55] Separately, early antibiotic exposure has also been associated with these long-term clinical outcomes.[53-56] However, it is unknown whether microbiota alterations specifically from GBS prophylaxis are associated with any long-term clinical outcomes. The impact of IAP on antibiotic resistance was inconsistent, with some evidence of an increase in the resistance of some antibiotics for some pathogens, with others showing no increase.[50 57-61] Globally, the overwhelming majority of GBS isolates are susceptible to penicillin,[62] however, in the US in 2005, 0.2% of GBS isolates were reaching the upper level of susceptibility for one or more beta-lactams.[63] In the era of antimicrobial resistance, such a widespread IAP strategy may be challenging in relation to the UK Department of Health and Social Care's antimicrobial resistance strategy

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to reduce unnecessary use of antibiotics.[64] Finally, there was a particular lack of information on the long-term outcomes of IAP. There was evidence from only one RCT using antibiotics for spontaneous preterm labour, which found that antibiotic use was moderately associated with serious consequences of functional impairment at seven years of age.[65] However, this study has applicability concerns as the antibiotics differed and were given for a longer duration.

Maternal anaphylaxis is another important harm to consider as it has potentially fatal consequences. However, as it is rare, it is difficult to explore in well-designed studies other than very large RCTs. In the US, four anaphylactic cases associated with GBS prophylaxis were reported since the introduction of guidelines in 1996 up to 2010.[66] In the UK, the rate of all-cause maternal anaphylaxis has been reported at 1.6 per 100,000 maternities (37 cases in three years, 11 due to penicillin) and one was a result of GBS prophylaxis. Two mothers (5%) died and 14 (38%) mothers and 7 (41%) neonates required intensive care admission.[67 68]

Other reported harms include neonatal respiratory distress,[69] maternal thrush,[70] and childhood atopic dermatitis.[71] IAP during labour may also limit birth choices for women and medicalise labour.[5] However, it is difficult to draw conclusions on the harms of screening as the evidence is based mainly on small observational studies, subject to bias, and/or have applicability concerns.

Uncertain evidence on screening effectiveness

The evidence on the clinical effectiveness of universal GBS screening is observational and focusses on incidence rather than clinical outcomes. There have been no randomised controlled trials (RCTs) assessing the effects of screening on the reduction of EOGBS incidence, clinical outcomes, or mortality. In the absence of RCTs, it is difficult to quantify the potential impact of adding screening to risk-based practice.

A systematic review of nine observational studies from Turkey, Australia, and the US found that the odds of EOGBS under universal screening were 55% lower than under risk-based prevention for all neonates and term neonates alone (three studies).[72] A recent study in a

UK maternity unit found that the rate of EOGBS fell from 0.99 per 1,000 live births in the risk-based period to 0.33 during the screening period; though, this was not statistically significant, and screening was instigated based on high incidence so there may have been regression to the mean.[73] ~~Additional analysis of mothers who were actually screened compared to the pre-screening period was reported as statistically significant (0.16 versus 0.99 per 1,000 live births, RR 0.16, p<0.05). However, the mothers who accepted screening may have been systematically different and authors acknowledged that there were statistically significant differences in several maternal characteristics between the screening and risk-based periods.~~ In a follow on study, the authors found that EOGBS incidence had increased to 1.79 per 1,000 live births after the cessation of screening, which was statistically significant when adjusting for ethnicity.[74] Most observational evidence shows no difference in EOGBS mortality between risk-based and screening prevention,[75-77] while the impact on long-term outcomes is unknown. However, these studies may be underpowered to detect differences in these rare outcomes.

The risk of bias from observational study designs is well-documented due to confounding and the inability to determine cause and effect.[78] [79] The majority of studies on GBS screening compare the incidence of EOGBS during a period of screening with a historical control period (i.e. risk-based prevention) that precedes it.[75-77] [80-83] Risk of bias is higher in these studies as participants in the study and control period are not contemporaneous so other changes occurring between these periods may contribute to results. The few observational studies that compare screening to concurrent controls often retrospectively compare women with a culture result to all other women;[84] [85] this may be biased due to the risk of misclassification and that people who accept screening are systematically different to those who do not.[72] [86] Finally, as most studies only assess culture-confirmed EOGBS, changes in disease incidence may actually reflect a decreased likelihood of culturing GBS in the laboratory because of antibiotics in neonates' blood as opposed to a true change.[87] This distorts the impact of screening and may explain why, in studies examining culture-confirmed EOGBS, a reduction in incidence is found between screening and risk-based prevention but in studies assessing mortality or all-cause neonatal sepsis, there is no difference. Studies exploring all-cause early-onset sepsis have been contradictory, [88-90] and

as mentioned above, studies on mortality may be underpowered to detect differences. As a result of the limitations, the effectiveness of universal GBS screening is uncertain.

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Conclusions

GBS infection is an important health problem and more work to understand and prevent neonatal disease is required. Universal GBS screening is a complex area and the current evidence of uncertainty about whether screening would do more good than harm highlights the problem with introducing a new screening programme. Selective maternal culture is not an accurate predictor of EOGBS disease in neonates. If a GBS screening programme is implemented, it would offer all term pregnant women the culture test, but around 99.8% of screen-positive mothers (and their babies) would be overdiagnosed and unnecessarily receive IAP. The harm from widespread IAP to thousands of pregnant women and their babies is unknown while the evidence on the benefit from screening is uncertain due to lower quality studies with serious limitations.

Recently, the Health Technology Assessment launched a call for an RCT assessing the effectiveness of GBS screening, which may address the uncertainty on the clinical benefits of screening. This should be complemented by research assessing the potential harms before we can be confident that universal screening is a safe undertaking. Additionally, research to more accurately identify the women at most risk of having a neonate with EOGBS could reduce the amount of overtreatment. Alternatively, advances are underway in the development of a GBS vaccine, which could avoid the concerns around screening and have the potential to prevent early and late onset GBS.[91]

Boxes

Key messages

1. Early-onset group B *Streptococcus* disease (< 7 days of life, EOGBS) is an important health problem and efforts should continue to better understand and prevent it.
2. A universal antenatal culture screening programme cannot currently be recommended.
3. Selective maternal culture is not an accurate test to predict EOGBS disease in neonates, and a lack of understanding about why some colonised mothers have a neonate with EOGBS limits the ability to identify a better approach.
4. The current approach would offer all term pregnant women the culture test and lead to around 99.8% of screen-positive women and their babies receiving unnecessary intrapartum antibiotic prophylaxis (IAP).
5. The addition of screening to risk-based prevention may reduce the incidence of EOGBS. However, a lack of high quality evidence on the benefits and harms of screening means that it is not possible to quantify the impact of universal GBS screening and assess whether IAP at such a large scale is a safe undertaking.

Figure caption / legend:

Figure 1. Natural history of GBS in a hypothetical cohort of term pregnant women in year 2000 (no national prevention guideline) and 2014 (risk-based national prevention guideline). Under no national prevention guideline, 126,159 term pregnant women were colonised with GBS, but only 205 term neonates developed EOGBS, meaning screening would overtreat 125,954 (99.8%) of women with IAP in labour.

Abbreviations: GBS Group B Streptococcus, EOGBS early-onset group B Streptococcus, intrapartum antibiotic prophylaxis, NPV Negative predictive value, PPV Positive predictive value

Notes: Due to the uncertainties of the data, the numbers should be treated cautiously for a sense of scale but not as exact estimates. Data estimates and sources:

a. Pregnant women available for screening in 2000 and 2014: All live births taken from the Office for National Statistics,[92] then elective caesarean sections and preterm births (<37 weeks) were removed from the cohort using HES estimates,[93 94] as elective caesarean sections are not at risk of EOGBS and preterm births are not eligible for screening. Note: Rate for preterm births in 2000 is taken from 2004-05.
b. Maternal GBS carriage: 22%.[31]
c. Number of EOGBS disease cases and mortality taken from British Paediatric Surveillance Unit study.[2 3 33]

d. Long-term disability: 8.7-15.8% of surviving EOGBS cases.[34-36]
e. Short-term EOGBS morbidity: Meningitis 13.2%; Sepsis 63.1%; Pneumonia 23.7%.[3]
f. EOGBS cases with maternal risk factors: 33-37% of EOGBS cases will have at least one risk factor for intrapartum antibiotic prophylaxis.[3]

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Conflict of interest declarations:

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Data sources and contributors:

The sources of information used to prepare this manuscript are from the NSC policy reviews of 2012 and 2016, in addition to the GBS model that was developed by the UK NSC, and studies on GBS epidemiology and screening published after the 2016 NSC review.

This piece of research and the completion of this manuscript involved a multi-disciplinary team of information specialists, epidemiologists, infectious disease, microbiology, and obstetrics and gynaecology consultants, screening and public health specialists, statisticians, and reviewers. AM, the Director of the UK NSC, JM, the Evidence Lead for the UK NSC, and CV, an Evidence Review Manager contributed to the writing of this manuscript but did not conduct any of the review processes or the synthesis and interpretation of the original reviews. The research team below conducted the 2016 NSC review for GBS.

FS has completed a PhD specialising in GBS screening and has previously conducted systematic reviews, including NSC reviews; FS secured funding, co-ordinated the review process, developed the protocol, created and applied the search strategy to collect the data, sifted, extracted, and quality assessed 20% of the articles, and synthesised the data for the 2016 review. FS also combined the evidence from the 2012 and 2016 NSC evidence reviews selecting the best available evidence for the purpose of this article and led the writing of

this manuscript. JG is an expert systematic reviewer specialising in screening and test accuracy and has previously conducted NSC reviews; JG carried out data sifting, extraction, quality assessment, and synthesis for all of the data for the 2016 review, reviewed the merging of data between the 2012 and 2016 evidence reviews, and reviewed the manuscript for redrafting. OU, CS and KF are also expert systematic reviewers who have conducted previous reviews for the NSC and health technology assessments for NICE; they contributed to protocol development for the 2016 review and reviewed this manuscript for redrafting. JP is a medical doctor with expertise in evidence-based medicine and systematic reviews who has conducted NSC reviews; JP reviewed this manuscript for redrafting. NM is an academic public health physician and epidemiologist with expertise in infectious disease control, ER is the lead public health microbiologist for East Midlands Pubic Health England, and CB is a consultant in infectious diseases and medical microbiology at Public Health England; they contributed to protocol development for the 2016 review and reviewed this manuscript for redrafting, providing expertise on infection and microbiology. BT is a clinician scientist, consultant obstetrician & gynaecologist and RCOG accredited subspecialist in reproductive medicine who has managed numerous patients with GBS in pregnancy; BT contributed to protocol development for the 2016 review and reviewed this manuscript for redrafting, providing obstetrics and gynaecology expertise. SJ is an academic support librarian and HF has studied the Masters in Screening course; they contributed to protocol development, search strategy development, and data collection of the 2016 review, and reviewed this manuscript for redrafting. AC is a clinical public health academic who heads the Division of Health Sciences at the Warwick Medical School and leads one of nine technology assessment review teams providing systematic reviews to NICE; AC contributed to protocol development for the 2016 review, and reviewed this manuscript for redrafting. STP is an associate professor of screening and test evaluation with wide experience in systematic reviews specialising in screening, including NSC reviews; STP secured the funding, co-ordinated the review process and developed the protocol for the 2016 review, and reviewed this manuscript for redrafting.

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