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ANALYSIS

Universal antenatal screening for group B streptococcus may cause more harm than good

Based on current evidence, routine screening for group B streptococcus colonisation in late pregnancy should not be introduced in the UK, as the potential harms of unnecessary treatment with antibiotics may outweigh the benefits, argue **Farah Seedat and colleagues**

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Key messages

- Early onset group B streptococcus (GBS) disease is an important health problem and efforts should continue to better understand and prevent it
- Selective maternal culture is not an accurate test to predict early onset GBS disease in neonates, and we don't know why some colonised mothers have a neonate with early onset GBS and others don't
- The current approach to screening would lead to 99.8% of screen positive women and their babies receiving unnecessary intrapartum antibiotic prophylaxis
- Lack of high quality evidence on clinical outcomes makes it impossible to quantify whether universal GBS screening would have any benefit and assess whether large scale intrapartum antibiotic prophylaxis is safe
- A universal antenatal culture screening programme cannot currently be recommended

Group B streptococcus (*Streptococcus agalactiae,* GBS) is the most common 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 infection) in around one of every 2000 live births.[2] To prevent early onset disease, intrapartum antibiotic prophylaxis, usually intravenous penicillin, is the recommended treatment internationally. The UK recommends a risk based strategy, whereby pregnant women presenting with risk factors for early onset GBS infection are offered antibiotic prophylaxis in labour.[3-6]

The media and politicians regularly call for universal antenatal screening for GBS as an alternative means of selecting women for prophylaxis. Advocates point to countries across Europe and North America where screening is recommended[7-19] and where reductions in early onset GBS infection have been observed.[20-22] But the evidence shows that the effectiveness of screening, using established screening criteria,[23] is uncertain and that screening has potential harms. Here, we explain why the UK National Screening Committee decided not to introduce routine screening in the UK[24 25]—namely, high levels of overtreatment, unknown potential hazards from screening and intrapartum antibiotic prophylaxis treatment, and uncertain benefit.

Impact of GBS

GBS is a Gram positive bacterium that colonises the gastrointestinal and genitourinary tracts in approximately 20% of pregnant women.[26 27] It usually causes no harm,[8] but if a woman is colonised at the time of labour, around 36% will transmit the bacteria to their newborn child.[28] Crucially, the majority of neonates colonised with GBS remain asymptomatic, but about 3% develop early onset infection.[28] In the UK and Republic of Ireland the incidence is estimated at 0.57 per 1000 live births (n=517).[2] Affected neonates present with sepsis in 63% of cases, pneumonia in 24%, meningitis in 13%,[29] and around 5-10% (n=27-38) die as a result.[30 2] Neurological

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impairment is reported in up to 16% of cases who survive infection,[31-33] though long term outcomes are not well researched. The true burden of early onset GBS infection is likely to be higher, as most of the research only describes cases confirmed by culture, and the infecting organism cannot be isolated in approximately half of neonatal sepsis cases.[34] It causes considerable morbidity and mortality.

A risk based strategy to prevent early onset GBS infection has been recommended in the UK since 2003.[3-6] Pregnant women presenting with preterm labour, GBS colonisation, a previous infant with GBS disease, GBS bacteriuria, intrapartum fever, or chorioamnionitis are offered intrapartum antibiotic prophylaxis.[3-6] But 65% of neonates with early onset GBS infection are born to mothers who have no risk factors and are therefore not eligible.[2]

Universal GBS screening

Screening comprises the collection of specimens from rectovaginal swabs at 35 to 37 weeks' gestation, which are processed using selective culture media to identify women colonised with GBS.[35] Screening would be offered to all pregnant women at term and could detect some of the 65% of neonates with early onset GBS infection born to mothers without risk factors.

Screening was first introduced in the US in 1996, where the incidence of culture confirmed early onset GBS infection was around 1.7 per 1000 live births.[21] After the 1996 recommendation that either risk based or screening strategies could be implemented, the incidence fell to 0.4 per 1000 in 2001. After the recommendation that screening should be implemented in 2002, the incidence fell further, to 0.3 per 1000 in 2004.[22] Screening has continued since and the incidence was estimated at 0.22 per 1000 live births in 2016.[36] Most countries that recommend screening have seen a similar reduction or stabilisation in the incidence of early onset disease,[20 37] though some have not.[38]

In the UK and Republic of Ireland, which have risk based prevention rather than screening, the incidence is much lower than in the US before screening, at 0.57 per 1000 live births in 2014-15.[2] But it has risen significantly from 0.48 per 1000 in 2000-01, before national guidelines were published.[39 2] [6] The reasons for this are unclear.

Overdiagnosis and potential harm

Given that only a small percentage of neonates born to women colonised with GBS get infected, the proposed screening programme would make many women eligible for prophylaxis whose babies would not have developed early onset infection if left untreated. Based on UK data, antenatal culture would correctly predict early onset infection in around two of every 1000 pregnant women (0.2%) with a positive result (fig 1). In 2000-01, under no national prevention guideline, 126 159 term pregnant women were colonised with GBS, but only 205 term neonates developed early onset infection, meaning screening would have led to overtreatment of 125 954 (99.8%) women in labour. Similarly, in 2014-15, under risk based prevention, 138 933 term pregnant women were colonised with GBS, but only 350 term neonates developed early onset infection, meaning screening would have led to overtreatment of 138 583 (99.75%) women in labour.

This positive predictive value of 0.2% would deliver an extremely high rate of false positive results, all of whom would be overtreated with intrapartum antibiotics. A cost effectiveness model published in 2007 also estimated that adding screening to risk based prevention would result in around 99.8% overtreatment and would increase antibiotic use in pregnancy from 11% to 27%.[44] Recently, an expert group convened by the UK National Screening Committee published a modelling exercise concluding that adding screening to a risk based strategy in the UK would result in an additional 1675-1854 women receiving intrapartum antibiotic prophylaxis to prevent one case of early onset GBS infection, and 24 065-32 087 to prevent one death due to early onset GBS infection.[43] Similarly, an Australian centre reported that 1191 women would need to be treated with intrapartum antibiotic prophylaxis to prevent one case of early onset GBS infection.[45] Although the models have some limitations because of evidence gaps, the estimates support the high levels of overtreatment that would occur.

Thus, examining the potential harms of GBS screening is important. A systematic review of 30 studies of intrapartum antibiotic prophylaxis found little evidence to quantify the potential harms to mothers and babies.[46] Although a range of adverse effects was investigated, the 11 studies in which the authors explicitly stated that they examined prophylaxis for GBS were observational and at risk of bias. The 13 randomised controlled trials at lower risk of bias investigated antibiotics and regimens different from GBS prophylaxis. Key findings were around changes in gut microbiota,[47-54] long term functional impairment,[55] and antibiotic resistance.[52 56-60]

There was consistent observational evidence that intrapartum antibiotic prophylaxis for GBS alters neonatal gut microbiota.[47-54] Changes to gut microbiota have been associated with metabolic problems (such as obesity and diabetes), atopic, inflammatory, and autoimmune problems (such as asthma and necrotising enterocolitis), and autism.[61-63] Early antibiotic exposure has also been associated with these long term clinical outcomes.[61-64] Causal links, however, have not been established, and we don't know whether microbiota alterations specifically from GBS prophylaxis are associated with any long term clinical outcomes.

The review found inconsistent results for the effect of prophylaxis on antibiotic resistance, with evidence of increased resistance for some antibiotics and pathogens and no increase for others.[52 56-60] Globally, the overwhelming majority of GBS isolates are susceptible to penicillin,[65] but in the US in 2005, 0.2% of GBS isolates were reaching the upper level of susceptibility for one or more β lactams.[66] Widespread prophylaxis may go against the Department of Health and Social Care for England's antimicrobial resistance strategy to reduce unnecessary use of antibiotics.[67] Finally, the review reported a lack of information on the long term outcomes of intrapartum antibiotic prophylaxis. Evidence from only one randomised controlled trial using antibiotics for spontaneous preterm labour showed that antibiotic use was moderately associated with serious consequences of functional impairment at 7 years of age.[55] This study has applicability concerns, however, as the antibiotics differed from those given for GBS and were given for a longer duration.

Maternal anaphylaxis is another important harm to consider, as it has potentially fatal consequences. But its rarity makes it difficult to explore in well designed studies other than very large randomised controlled trials. In the US, four cases of anaphylaxis associated with GBS prophylaxis were reported after the introduction of guidelines in 1996 up to 2010.[68] The rate of all cause maternal anaphylaxis in the UK has been reported at 1.6 per 100 000 maternities—37 cases in three years, 11 due to penicillin and one the result of GBS prophylaxis. Two mothers (5%) died; 14 (38%) mothers and seven (41%) neonates required intensive care admission.[69 70]

Other reported harms include neonatal respiratory distress,[71] maternal thrush,[72] and childhood atopic dermatitis.[73] Antibiotic prophylaxis in labour may also limit birth choices for women and contribute to the medicalisation of labour.[4] Drawing conclusions on the harms of screening is difficult, however, as the evidence is based mainly on small observational studies, subject to bias, or has applicability concerns.

Uncertain evidence on screening effectiveness

The evidence on clinical effectiveness of GBS screening is observational and focuses on incidence rather than clinical outcomes. No randomised controlled trials have assessed the effects of screening on the incidence of early onset GBS infection, clinical outcomes, or mortality. In the absence of randomised controlled trial data, quantifying the potential impact of adding screening to risk based practice is difficult. Most observational evidence shows no difference in mortality due to early onset GBS infection between risk based and screening prevention,[74-76] and we do not know the difference in the long term clinical outcomes of early onset GBS infection between the two strategies. These studies, however, may be underpowered to detect differences in these rare outcomes. Studies examining all cause early onset sepsis have been contradictory.[77-79]

A systematic review of nine observational studies from Turkey, Australia, and the US found that the odds of early onset GBS infection under universal screening were 55% lower than under risk based prevention for all neonates and for term neonates (three studies).[80] A 2017 study in a UK maternity unit found that the rate of early onset GBS infection fell from 0.99 per 1000 live births in the risk based period to 0.33 per 1000 in the screening period, although this was not statistically significant, and screening was instigated based on high incidence so there may have been regression to the mean.[81] In a follow-on study, the authors found that incidence of early onset GBS infection had risen to 1.79 per 1000 live births after screening was stopped, which was statistically significant when adjusting for ethnicity.[82]

The well documented risk of bias in observational study designs is due to confounding and the inability to determine cause and effect.[83 84] The majority of studies on GBS screening compare the incidence of early onset infection in a period of screening against a historical control period (that is, risk based prevention).[74-76 85-88] Risk of bias is higher in these studies because participants in the two arms are not contemporaneous, so other differences between these periods may contribute. The few observational studies that compare screening with concurrent controls often retrospectively compare women who have a culture result to all other women[89 90]; this may be biased due to the risk of misclassification and because people who accept screening are systematically different from those who do not.[80 91] Finally, as most studies only assess early onset GBS infection confirmed on culture, changes in disease incidence may actually reflect a decreased likelihood of culturing GBS in the laboratory, owing to the presence of antibiotics in neonates' blood.[92] This could distort the effect of screening and may explain why studies examining early onset GBS infection confirmed on culture find a reduction in incidence between screening and risk based prevention, when studies assessing mortality or all cause neonatal sepsis find no difference. Because of these limitations, the effectiveness of universal GBS screening is uncertain.

Conclusions

GBS infection is an important health problem, and we need more work to understand and prevent neonatal disease. Universal GBS screening is a complex area, and the current uncertain evidence about whether screening would do more good than harm emphasises the problem of introducing a new screening programme. Selective maternal culture is not an accurate predictor of early onset GBS disease in neonates. If a GBS screening programme was implemented, it would offer all term pregnant women the culture test, but around 99.8% of mothers who screen positive (and their babies) would experience overdiagnosis and would be offered intrapartum antibiotic prophylaxis unnecessarily. The harm from widespread prophylaxis to thousands of pregnant women and their babies is unknown, and the evidence for benefit from screening is uncertain owing to lower quality studies with serious limitations.

The Health Technology Assessment programme recently launched a call for a randomised controlled trial assessing the effectiveness of GBS screening, which may tackle this uncertainty. But we also need research assessing the potential harms before we can be confident that screening is safe. Being able to more accurately identify the women at most risk of having a neonate with early onset GBS infection could reduce the amount of overtreatment. Alternatively, advances are under way in the development of a GBS vaccine, which would affect all antibiotic based preventive strategies and have the potential to prevent early and late onset GBS infection.[93]

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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 Public 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 and 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. ST-P is an associate professor of screening and test evaluation with wide experience in systematic reviews specialising in screening, including NSC reviews; ST-P secured the funding, coordinated the review process, developed the protocol for the 2016 review, and reviewed this manuscript for redrafting. ST-P is the guarantor.

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Figure

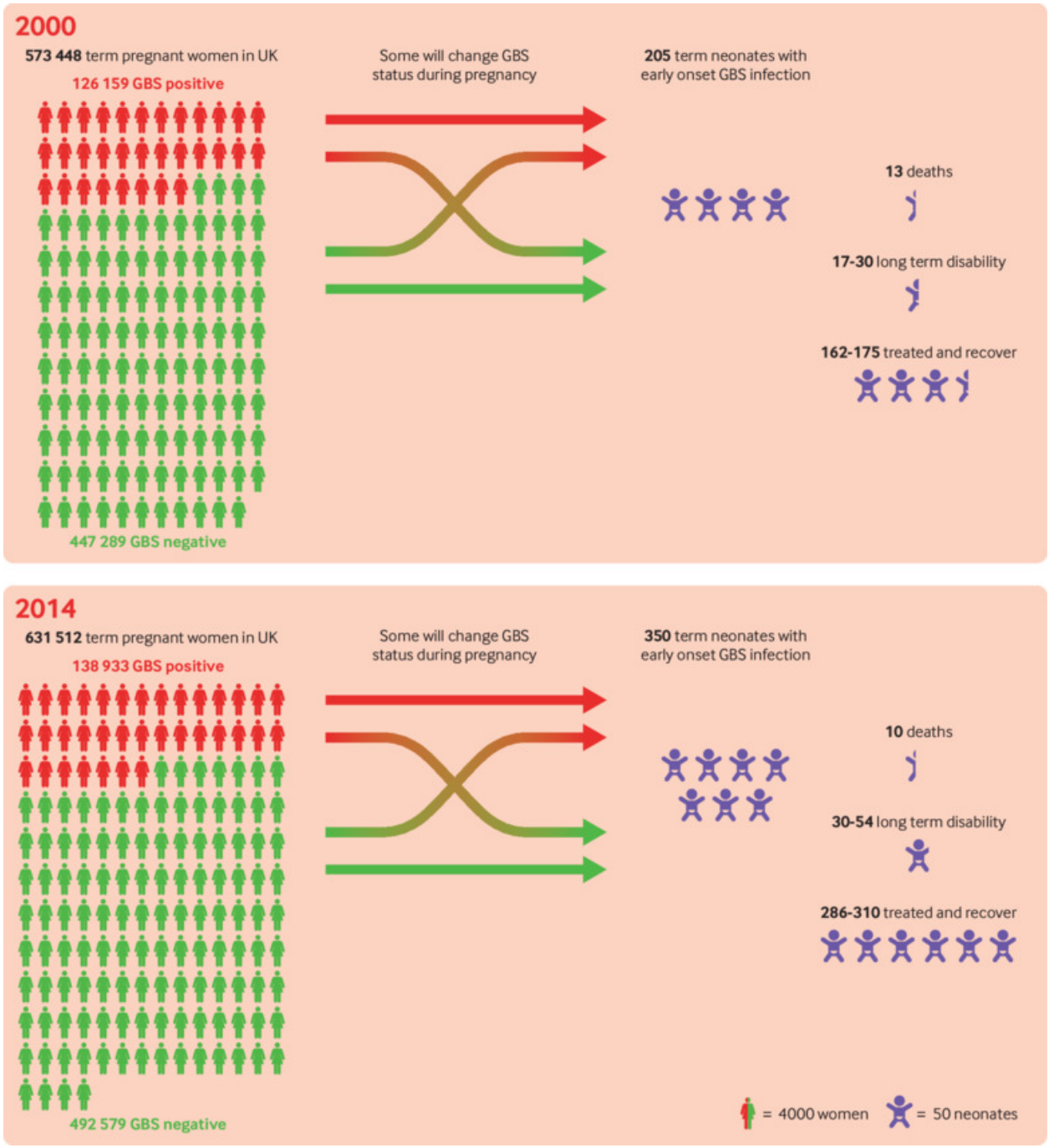

Fig 1 Natural history of GBS in a hypothetical cohort of term pregnant women in 2000 (no national prevention guideline) and 2014 (risk based national prevention guideline). GBS=group B streptococcus. Owing to the uncertainties of the data, the numbers should be treated cautiously for a sense of scale but not as exact estimates. Data estimates and sources: Pregnant women available for screening in 2000 and 2014: all live births taken from the Office for National Statistics,[40] then elective caesarean sections and preterm births (<37 weeks) were removed from the cohort using Hospital Episodes Statistics estimates,[41 42] as babies born by elective caesarean section are not at risk of early onset GBS infection and preterm births are not eligible for screening. Rate of preterm births in 2000 is taken from 2004-05. Maternal GBS carriage: 22%.[43] Number of cases of early onset infection and mortality taken from the British Paediatric Surveillance Unit study.[29 30 39] Long term disability: 8.7-15.8% of surviving early onset cases.[31-33] Short term early onset GBS infection morbidity: meningitis 13.2%, sepsis 63.1%, pneumonia 23.7%.[29] Early onset GBS infection cases with maternal risk factors: 33-37% of cases will have at least one risk factor for intrapartum antibiotic prophylaxis.[29]