To screen or not to screen women for Group B Streptococcus (Streptococcus agalactiae) to prevent early onset sepsis in newborns: recent advances in the unresolved debate

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Abstract: Streptococcus agalactiae, also known as Group B streptococcus (GBS) is the commonest cause of early onset sepsis in newborns in developed high-income countries. Intrapartum antimicrobial (antibiotic) prophylaxis (IAP) is recognized to be highly effective in preventing early onset Group B sepsis (EOGBS) in newborns. The key controversy is about the strategy that should be used to identify mothers who should receive IAP. There are two strategies that are followed in developed countries: screening-based or risk-factor-based identification of women requiring IAP. The debate regarding which of the two approaches is better has intensified in the recent years with concerns about antimicrobial resistance, effect on newborn’s microbiome and other adverse effects. In this review, we have discussed some of the key research papers published in the period 2015–2019 that have addressed the relative merits and disadvantages of screening versus risk-factor-based identification of women requiring IAP. Although screening-based IAP appears to be more efficacious than risk-based IAP, IAP-based prevention has several limitations including ineffectiveness in prevention of late-onset GBS infection in babies, premature and still births, impact of IAP on neonatal microbiota, emergence of antimicrobial resistance and difficulties in implementing IAP-based strategies in middle and low income countries. Alternative strategies, principally maternal immunization against GBS would circumvent use of IAP. However, no licensed vaccines are currently available for use.

Keywords: Group B Streptococcus, intrapartum antimicrobial prophylaxis, screening, risk factor
prophylaxis and the absence of such an effect on late onset disease. It is estimated that worldwide about 22 million women carry GBS with an estimated 410,000 infections in newborns every year, with at least 147,000 still births and infant deaths globally.

Furthermore, the same study estimated that there were 33,000 cases of invasive GBS disease in pregnant or postpartum women, and 57,000 foetal infections/stillbirths. Up to 3.5 million preterm births may be attributable to GBS.

Currently, it is widely agreed that the only effective way to prevent EOGBS is to give intrapartum antibiotic prophylaxis (IAP) to the mothers. IAP has an efficacy of >80% in prevention of EOGBS. However, there is considerable disagreement and debate about the best way of identifying women who need IAP. In tandem, there is an emerging debate regarding the impact of IAP on the microbiome of the newborn.

In this article, we discuss some of the key research papers published in the period 2015–2019 that have addressed the relative merits and disadvantages of screening versus risk-factor-based strategies for identification of women requiring IAP. Where older papers are cited, it was done to set the context for more recent papers. Importantly, the papers were selected to provide a general overview of the debate rather than to undertake a systematic review or in-depth discussion of the components or variations of the two strategies. We have also excluded systematic reviews or studies based on meta-analysis of trials. Discussion regarding vaccines for prevention of EOGBS and effect of IAP on the neonatal microbiome is outside the scope of this paper.

**EOGBS prevention strategies used worldwide**

Until recently there was no review of EOGBS prevention strategies used worldwide. A recent paper has addressed this gap in knowledge. Le Doare et al. reviewed GBS screening policies and IAP implementation worldwide. They received policy information from nearly half the countries surveyed [95 of 195 (49%)]. Of these, over 60% had an IAP policy; a majority used screening (58%) while the rest used the presence of risk factors to guide IAP. Coverage was considerably higher with screening (80%) compared with risk-factor-based IAP (29%). The authors concluded that there was considerable heterogeneity in IAP screening policies and coverage worldwide. Screening-based guidelines used in many parts of the world are derived from EOGBS Prevention Guidelines recommended by Centers for Disease Control in the US (CDC).

While the guidelines primarily recommend IAP based on antenatal GBS screening, they also recommend giving IAP to women with risk factors such as GBS bacteriuria during pregnancy or a history of a previous GBS-infected newborn. In addition, CDC recommends that if the prenatal GBS culture result is unknown when labour starts, intrapartum antibiotic prophylaxis is indicated for women who have risk factors for GBS early onset disease (EOD). These include at-risk women who present in labour with a substantial risk of preterm birth, who have preterm prelabour rupture of membranes (PPROM) or rupture of membranes for 18 or more hours at term, or who present with intrapartum fever [temperature 100.4°F (38°C) or higher]. Thus the CDC guidelines recommend a ‘combined’ approach with emphasis on screening.

CDC guidelines state that the culture method is the gold standard for identifying GBS. The guidelines also recommend using selective enrichment broth prior to culturing on solid agar media. Cultures can take up to 48 to 72 h and therefore can be done only during the antenatal period. It is now well recognised that antenatal cultures do not accurately predict intrapartum GBS carriage.

In the past decade, the availability of rapid nucleic acid amplification tests (NAATs) with very high specificity and sensitivity has made it possible to test women who have not been previously screened or who present in pre-term labour. However, NAATs require expensive equipment and reagents that may not be available in resource poor countries. The biggest disadvantage of NAATs is that they do not provide information regarding antibiotic susceptibility of the GBS strains, which is important for deciding the antibiotic treatment options in penicillin allergic women and surveillance of antimicrobial resistance.
Efficacy of screening- versus risk-based strategy: which of these two strategies is better?

To this day, there are no randomised controlled trials to compare the efficacy of the two strategies. Recently, the National Institute of Health Research (NIHR) commissioned a cluster randomized trial in the UK to compare the effectiveness of the two strategies. The NIHR-funded study (GBS-3 Trial) will measure the effectiveness of two tests to identify group B streptococcus in late pregnancy or labour compared with the current UK approach of identifying pregnant women with ‘risk factors’ for their newborn developing the infection. The trial will include over 80 hospitals in the UK. The trial was due to commence in April 2020 but recruitment has been delayed due to the Covid 19 pandemic (https://www.nihr.ac.uk/news/new-screening-trial-aims-to-improve-detection-and-treatment-for-group-b-strep-in-pregnant-women/20283 accessed 03-05-2020).

In the absence of randomised trials, virtually all the reports published thus far are based on observational ‘before–after’ studies. The following are a brief description of some of the studies published recently.

In Germany, the national guidelines changed from risk factor based IAP (2000–2008) to antenatal screening based IAP 2009. For the period 2009–2010, a prospective active surveillance study assessed the incidence of invasive GBS infections in infants aged 0–90 days. The authors of the study captured the data from two separate, independent systems (paediatric reporting versus laboratory reporting); and compared their results with those from a previous study by employing an equivalent design (2001–2003). They reported a 32% reduction in GBS incidence, from 0.47 per 1000 live births ($n=679$) in 2001–2003, to 0.34 per 1000 live births ($n=450$) in 2009–2010. The authors concluded that this decline was due to reduced number of EOGBS cases in children under 1 week of age.12

In the US, where screening-based IAP is used, the incidence of EOGBS has continued to fall. Recently, Nanduri et al. reported that from 2006 to 2015, EOGBS incidence declined significantly from 0.37 to 0.23 per 1000 live births ($p<0.001$). Interestingly, among the mothers of 1277 infants with EOGBS, nearly half (48.3%) had no indications for IAP and did not receive it. Moreover, nearly 22% did not receive IAP despite having indications. The authors concluded that while there were still gaps in implementation of IAP, other strategies were necessary to prevent EOGBS in babies of mothers who did not have indications for IAP.13 Improved implementation supported by clinical decision systems and regular audits are likely to be helpful in ensuring mothers at risk are given IAP. Most of the mothers considered to be not at risk had negative antenatal screening results. It is possible that intrapartum screening using nucleic acid amplification methods may detect GBS carriage in at risk mothers more accurately compared with antenatal screening. The ultimate solution to prevent EOGBS and LOGBS in all infants including in premature babies will be an effective vaccine, when it becomes available.

In Australia, maternity units can choose to either use screening-based or risk-based IAP. A recent observational retrospective cohort study in a local health district in New South Wales studied 62,281 women who had 92,055 pregnancies resulting in 93,584 live born babies in the period 2013 to 2016; 31% of pregnancies were either not screened or were not given IAP despite the mother being colonised with GBS. A total of 18 babies developed EOGBS with an estimated incidence/1000 live births of 0.35 (95% CI: 0.07–0.63) in 2006 and 0.1 (95% CI: 0–0.2) in 2016. Of 10 term babies with EOGBS, 7 were born to mothers who screened negative. Data did not provide evidence of difference in rates of EOGBS between screened and unscreened pregnancies. The authors concluded that no change was detected in rates of EOGBS over time and there was no difference in rate of EOGBS in babies of screened and unscreened mothers.16
In New Zealand 2004, an expert multidisciplinary group reviewed the evidence on IAP and the results of a national two-year surveillance study of EOGBS in the period 1998–1999. The group recommended a risk factor-based prevention strategy for prevention of EOGBS in New Zealand. The New Zealand Paediatric Surveillance Unit completed a repeat survey of EOGBS infection in 2011. This survey showed that the incidence of EOGBS had halved in the 10 years since the first survey, from 0.5 per 1000 live births to 0.26 per 1000 (95% CI: 0.18–0.37) live births. The study also found there were missed opportunities for preventing GBS infection. As a result, national guidelines in New Zealand continue to recommend risk based IAP and specifically do not recommend screening based IAP.17

In 2014–15, a similar survey by the British Paediatric Surveillance Unit prospectively determined the burden of invasive group B streptococcal disease in infants younger than 90 days in the UK and Ireland. The authors found that incidence of EOGBS (n = 517) was 0.57 per 1000 livebirths (95% CI: 0.52–0.62) and observed that the incidence of invasive infant group B streptococcal disease in the UK and Ireland had increased since a comparable study done in 2000–2001. They concluded that the burden of EOGBS had not declined even after the introduction of national guidelines in 2003 that recommends risk-based IAP. They concluded that new strategies were required for prevention of invasive GBS infection.3

While studies on GBS prevention were commonly reported from the developed Western world, in the recent years, a few studies have been published that describe the efficacy of IAP in other parts of the world including Asia and Africa.

In a retrospective cohort study, 21.8% of 114,000 screened pregnant women in Hong Kong were colonised with GBS. Most eligible women opted for screening and women colonized with GBS received IAP. There were 29 cases of EOGBS. Compared with clinical risk-based screening, EOGBS incidence decreased after introduction of universal screening (1 versus 0.24 per 1000 births, p < 0.001).18

In Saudi Arabia, Luhidan et al., determined the incidence and burden of GBS infection among neonates and its association with maternal GBS screening in a 13-year period study from 2004 to 2016. The authors reported that in the 13 years, in 108,609 live births, 38 babies (0.39/1000 live births) had EOGBS. The annual incidence in 2015 and 2016 was significantly higher than in any previous year (p < 0.0001), coinciding with the discontinuation of routine universal maternal GBS screening. They found that neonates of unscreened mothers were more likely to present with EOD (p = 0.005). They concluded that incidence of neonatal GBS infection in Saudi Arabia is similar to the worldwide incidence. Importantly, like Rao et al., they observed that discontinuation of universal antenatal screening was significantly associated with an increase in EOGBS incidence.19

While Africa has the highest burden of EOGBS infection in the world, there are continuing challenges in implementing intrapartum prophylaxis, both using risk-based or screening-based strategies due to limited resources.20 It is clear that only vaccines can provide a realistic solution for prevention of GBS related infant mortality in most parts of Africa. Maternal GBS vaccination could be a safe, cost-effective strategy and prevent 30–55% deaths in low-income sub-Saharan Africa.21

In summary, many observational studies appear to find a screening-based strategy more efficacious in preventing EOGBS than a risk-based strategy. However, experience in New Zealand suggests that risk-based strategy can be effective,12 although in the UK, the EOGBS rates have gone up despite the introduction of risk-based strategy in 2003.13

Adverse effects

Today the principal debate regarding the relative merits of the two strategies has shifted from efficacy to adverse effects of IAP. While both strategies offer IAP to mothers, it is argued that a screening-based strategy exposes more mothers to antibiotics than risk-based strategy and as a result, are more likely to suffer adverse effects.22

Does screening-based strategy lead to more women getting IAP than with a risk-based strategy?

A key modelling study based on primary data by Kaambwa et al. showed that a similar number of patients would receive antibiotics using either strategy. Of the 1400 women recruited into the study, 22.1% women had risk factors whereas
21% screened women were GBS carriers. The sensitivity and specificity of risk-based IAP were 31% and 80%, respectively, compared with antenatal screening cultures which had sensitivity and specificity of 76% and 95%, respectively. These findings indicate that just as many women would receive IAP with both strategies but using a risk-based strategy, IAP would be unnecessarily given to 69% of women who are not GBS carriers. Furthermore, the authors concluded that risk-based IAP was not cost effective. In a recent modelling study commissioned by the National Screening Committee in England, Bevan et al. concluded that with the limited evidence base available, the model suggested that the major reduction in EOGBS would occur in babies born to low-risk women where the clinical outcome of EOGBS is likely to be less severe. The model proposed that the antenatal screening would have very limited effect on mortality and severe disability due to EOGBS and lead to excessive use of antibiotics.24

Observational studies differ considerably in estimating the number of women who need to be given IAP to prevent a single case of EOGBS. In 2007, Angstetra et al. in Australia reported the number of women needed to be given IAP was 1191 and 5704 women were screened to prevent one case of early-onset GBS disease. More recently, in their modelling study, Beven et al. reported that compared with risk-based IAP, screening-based IAP would result in an additional 1675 to 1854 women receiving IAP to prevent one EOGBS case and as many as 24,065 to 32,087 women receiving IAP to prevent one EOGBS death.24

Turning to adverse effects, Seedat et al. observed in a systematic review that despite a wide range of adverse events occurring following IAP, the evidence was inconsistent and at high risk of bias. Seven observational studies showed that IAP for maternal GBS colonization altered the infant microbiome but significance of these changes on clinical outcomes was not described and, as such, the importance of these alterations is unclear. The authors noted there was also observational evidence for increased antimicrobial resistance; however, studies were at high or unclear risk of bias.22 Millions of doses of penicillin or ampicillin have been given as IAP clinically significant resistance to penicillin or ampicillin has not been reported. Although penicillin-resistant GBS have been reported in respiratory isolates from patients in Japan, they were not detected in GBS strains isolated from mothers or their babies.26 Recently however, Moroi et al. determined the minimum inhibitory concentration of seven β-lactam antibiotics for 477 GBS isolates derived from vaginal/rectal swabs from pregnant women. All the 477 isolates were susceptible to penicillin G and ampicillin. Five isolates showed reduced ceftibuten susceptibility. Each of these isolates possessed a single amino acid substitution in the penicillin binding protein, PBP2X, and some of the substitutions which had been previously found in GBS strains with reduced penicillin susceptibility. It is unclear if this will eventually lead to penicillin resistance in GBS.27

A major concern has been that IAP increases the risk of anaphylactic reaction to penicillin. To date, there have been very few confirmed reports of anaphylaxis in women who received penicillin or ampicillin as IAP. In this context, a recent study by McCall et al. is important.28 They estimated the incidence of anaphylaxis in pregnancy and described the management and outcomes in the UK using the UK Obstetric Surveillance System. All pregnant women who had anaphylaxis between 1 October 2012 and 30 September 2015 were included. There were 37 confirmed cases of anaphylaxis in pregnancy but only one due to IAP given for prevention of EOGBS. This anaphylactic reaction did not prove to be fatal for the mother or the baby. The authors concluded that the overall low incidence was reassuring given the large proportion of the pregnant population that receive prophylactic antibiotics during delivery.

Conclusion
Overall, we believe that screening-based IAP is more efficacious than risk-based IAP and is the preferred option in developed countries. Rapid availability of results using NAATs may enable use of these tests to accurately target IAP to GBS colonized women in the intrapartum period. At a practical level, there are major challenges in implementing screening-based IAP in low income countries with poor laboratory support. In these countries, clinical risk-based IAP may be preferable albeit with lower efficacy. It must be acknowledged that IAP-based prevention has many limitations. IAP is not effective in prevention of late-onset GBS infection in babies, premature
deliveries and still births due to GBS infection. There are also growing concerns regarding the possible impact of IAP on neonatal microbiota and emergence of antimicrobial resistance. While resistance to clindamycin has risen considerably in the recent years, GBS strains from pregnant women have remained susceptible to penicillin. Reassuringly, a recent study from the UK has shown that anaphylactic reaction to penicillin is very rare in women who received IAP.

Alternative strategies, principally maternal immunization against GBS would avoid use of IAP. A recent modelling study estimated that a maternal vaccine with 80% efficacy and 90% coverage could prevent 107,000 (Uncertainty Range, 20,000–198,000) stillbirths and infant deaths.3

Unfortunately, no vaccines are currently available for routine use. Until such time vaccines are available, IAP-based prevention of EOGBS is the only game in town!

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GGR and PK contributed equally to writing and reviewing the final manuscript.

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References
1. Heath PT and Jardine LA. Neonatal infections: group B streptococcus. BMJ Clin Evid 2010; 2010:323
2. Schuchat A. Epidemiology of group B streptococcal disease in the United States: shifting paradigms. Clin Microbiol Rev 1998; 11: 497–513.
3. O’Sullivan CP, Lamagni T, Patel D, et al. Group B streptococcal disease in UK and Irish infants younger than 90 days, 2014–15: a prospective surveillance study. Lancet Infect Dis 2019; 19: 83–90.
4. Nanduri SA, Petit S, Smelser C, et al. Epidemiology of invasive early-onset and late-onset group B streptococcal disease in the United States, 2006 to 2015: Multistate laboratory and population-based surveillance. JAMA Pediatr 2018; 30333: 224–233.
5. Seale AC, Bianchi-Jassir F, Russel NJ, et al. Estimates of the burden of group B streptococcal disease worldwide for pregnant women, stillbirths, and children. Clin Infect Dis 2017; 65: S200–S219.
6. Fairlie T, Zell ER and Schrag S. Effectiveness of intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal disease. Obs Gynecol 2013; 121: 570–577.
7. Seedat F, Geppert J, Stinton C, et al. Universal antenatal screening for group B streptococcus may cause more harm than good. BMJ 2019; 364:1463.
8. Cassidy-Bushrow AE, Sitarik A, Levin AM, et al. Maternal group B Streptococcus and the infant gut microbiota. J Dev Orig Health Dis 2016; 7: 45–53.
9. Le Doare K, O’Driscoll M, Turner K, et al. Intrapartum antibiotic chemoprophylaxis policies for the prevention of group B streptococcal disease worldwide: systematic review. Clin Infect Dis 2017; 65: S143–S151.
10. ACOG COMMITTEE OPINION Committee on Obstetric Practice. Early-onset Group B streptococcal disease. Obstet Gynecol 2020; 135: 510–372.
11. Alfa MJ, Sepehri S, De Gagne P, et al. Real-time PCR assay provides reliable assessment of intrapartum carriage of group B Streptococcus. J Clin Microbiol 2010; 48: 3095–3099.
12. Wicker E, Lander F, Weidemann F, et al. Group B streptococci: declining incidence in infants in Germany. Pediatr Infect Dis J 2019; 38: 516–519.
13. Nanduri SA, Petit S, Smelser C, et al. Epidemiology of invasive early-onset and late-onset group B streptococcal disease in the United States, 2006 to 2015. JAMA Pediatr 2019; 173: 224.
14. Gopal Rao G, Nartey G, McAree T, et al. Outcome of a screening programme for the prevention of neonatal invasive early-onset group B Streptococcus infection in a UK maternity unit: an observational study. BMJ Open 2017; 7: e014634.
15. Gopal Rao G, Townsend J, Stevenson D, et al. Early-onset group B Streptococcus (EOGBS) infection subsequent to cessation of screening-based intrapartum prophylaxis: findings of an observational study in West London, UK. BMJ Open 2017; 7: e018795.

16. Braye K, Foureur M, de Waal K, et al. Group B streptococcal screening, intrapartum antibiotic prophylaxis, and neonatal early-onset infection rates in an Australian local health district: 2006-2016. PLoS One 2019; 14: e0214295.

17. Darlow BA, Voss L, Lennon DR, et al. Early-onset neonatal group B streptococcus sepsis following national risk-based prevention guidelines. Aust New Zeal J Obstet Gynaecol 2016; 56: 69–74.

18. Ma TWL, Chan V, So CH, et al. Prevention of early onset group B streptococcal disease by universal antenatal culture-based screening in all public hospitals in Hong Kong. J Matern Neonatal Med 2018; 31: 881–887.

19. Al Luhidan L, Madani A, Albayan EA, et al. Neonatal group B streptococcal infection in a tertiary care hospital in Saudi Arabia. Pediatr Infect Dis J 2019; 38: 731–734.

20. Nishihara Y, Dangor Z, French N, et al. Challenges in reducing group B Streptococcus disease in African settings. Arch Dis Child 2017; 102: 72–77.

21. Russell LB, Kim SY, Cosgriff B, et al. Cost-effectiveness of maternal GBS immunization in low-income sub-Saharan Africa. Vaccine 2017; 35: 6905–6914.

22. Seedat F, Stinton C, Patterson J, et al. Adverse events in women and children who have received intrapartum antibiotic prophylaxis treatment: a systematic review. BMC Pregnancy Childbirth 2017; 17: 247.

23. Kaambwa B, Bryan S, Gray J, et al. Cost-effectiveness of rapid tests and other existing strategies for screening and management of early-onset group B streptococcus during labour. BJOG An Int J Obstet Gynaecol 2010; 117: 1616–1627.

24. Bevan D, White A, Marshall J, et al. Modelling the effect of the introduction of antenatal screening for group B Streptococcus (GBS) carriage in the UK. BMJ Open 2019; 9: e024324.

25. Angstetra D, Ferguson J and Giles WB. Institution of universal screening for Group B streptococcus (GBS) from a risk management protocol results in reduction of early-onset GBS disease in a tertiary obstetric unit. Aust New Zeal J Obstet Gynaecol 2007; 47: 378–382.

26. Seki T, Kimura K, Reid ME, et al. High isolation rate of MDR group B streptococci with reduced penicillin susceptibility in Japan. J Antimicrob Chemother 2015; 70: 2725–2728.

27. Moroi H, Kimura K, Kotani T, et al. Isolation of group B Streptococci with reduced β-lactam susceptibility from pregnant women. Emerg Microbes Infect 2019; 8: 2–7.

28. McCall SJ, Bunch KJ, Brocklehurst P, et al. The incidence, characteristics, management and outcomes of anaphylaxis in pregnancy: a population-based descriptive study. BJOG 2018; 125: 965–971.