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Bertie Geng

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The Cost-Effectiveness of Culture vs NAAT Based Screening of Pregnant Women for Group B Streptococcus to Reduce Early-Onset Sepsis of the Newborn

A Thesis Submitted to the
Yale University School of Medicine
In Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Bertie Geng
2020
ABSTRACT

THE COST-EFFECTIVENESS OF CULTURE VS NAAT BASED SCREENING OF PREGNANT WOMEN FOR GROUP B STREPTOCOCCUS TO REDUCE EARLY-ONSET SEPSIS OF THE NEWBORN

Bertie Geng, Xiao Wu, Ajay Malhotra, Yogangi Malhotra, and Jessica Illuzzi. Department of Obstetrics, Gynecology & Reproductive Sciences, Yale University School of Medicine, New Haven, CT.

While great progress has been made to reduce its incidence, group B streptococcus (GBS) is still a leading cause of neonatal disease. Current standard of care recommends antepartum rectovaginal GBS culture of all pregnant women at 36 weeks of gestation in order to identify candidates for intrapartum prophylaxis to reduce vertical transmission. The purpose of the study is to assess three alternative nucleic acid amplification (NAAT) screening strategies for GBS: antepartum NAAT at 36 weeks, intrapartum NAAT, or a combined intrapartum and antepartum approach in which patients with penicillin allergies undergo antepartum culture screening and all other patients undergo intrapartum NAAT screening. A decision tree model was created using TreeAge Pro Suite 2018 where values of input parameters (probabilities, costs, and utilities) were obtained from published literature. All cost estimates were reported in 2019 U.S. dollars. Base case analysis, one-way sensitivity analyses, and a Monte Carlo simulation were conducted to assess the cost-effectiveness of NAAT at 36 weeks, intrapartum NAAT, and combined intrapartum/antepartum screening, relative to antepartum culture screening at 36 weeks. An incremental cost-effectiveness ratio (ICER) below $100,000 per quality-adjusted life year (QALY) was considered cost-effective. The base case analysis showed that, among the three proposed NAAT strategies, the combined antepartum and intrapartum approach as well as the intrapartum approach are cost-effective, with an ICER of $92,109.56 per QALY and $97,791.02 per QALY, respectively, compared to antepartum culture based screening. One way sensitivity analysis showed that the intrapartum NAAT approach was more favorable than antepartum culture when the GBS carrier prevalence was below 22%, the percentage of women who
changed GBS carrier status from negative to positive (negative to positive conversion rate) was above 3.8% and the intrapartum NAAT error rate was less than 5%. The Monte Carlo simulation showed that the combined approach was the optimal strategy in 49% of iterations while antepartum culture was the optimal approach in 51% of iterations. Cost-effectiveness acceptability curve showed that the combined approach had a 0.48 probability of being cost effective compared to antepartum culture at a willingness-to-pay (WTP) threshold of $100,000 per QALY. Intrapartum screening methods involving NAAT could potentially be cost-effective interventions to reduce the morbidity and mortality of GBS disease. Given limited data about the efficacy of clindamycin and vancomycin in women with anaphylactic penicillin allergy, further study is required to determine the optimal strategy to reduce early onset GBS sepsis of the newborn.
ACKNOWLEDGEMENTS

A great big thank you goes to Xiao Wu. Xiao, thank you for all your patience and all your support, not only for this project but throughout the course of our friendship. I can easily say that this project wouldn’t have happened without you.

Thank you to Drs. Ajay and Yogangi Malhotra. Thank you for being wonderful teachers and introducing me to the world of clinical research. I really appreciate all the time you two have invested into helping and mentoring me over my entire time at Yale Medical School.

A huge thank you to Dr. Illuzzi, Dr. Illuzzi, thank you so much for being such a kind and understanding mentor. Thank you so much for being willing to be my thesis advisor when I approached you at the beginning of fourth year and thank you so much for all the time that you’ve spent supporting my entry into the world of OB-GYN. I really can’t adequately express how much your constant encouragement has meant and continues to mean to me.

And last but certainly not least, thank you, Myron.
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INTRODUCTION

Importance of Group B Streptococcus

Group B streptococcus (GBS) is currently the most common infectious cause of morbidity and mortality among infants.\textsuperscript{1,2} GBS emerged as a leading cause of neonatal disease in the 1970s with initial case-series reporting fatality rates of up to 50%.\textsuperscript{3} Although overall fatality rates have since decreased to 4-6% with improvements in neonatal care, mortality remains around 20% for preterm infants.\textsuperscript{4,5} Symptoms of GBS early-onset disease (EOD) present within the first week of life and most often in the first 12-48 hours.\textsuperscript{6} These symptoms frequently include respiratory distress, apnea, and other signs of sepsis and pneumonia.\textsuperscript{7-9} In contrast, GBS late-onset disease (LOD) presents between 7 and 89 days of life, often with bacteremia and meningitis.\textsuperscript{10,11} Both early and late onset disease of the newborn may result in significant morbidity and prolonged hospitalization as well as long term sequelae, including neurocognitive and sensory deficits.\textsuperscript{12,13}

Risk Factors

The primary risk factor for GBS EOD is intrapartum vaginal-rectal maternal colonization with GBS.\textsuperscript{14-16} GBS, also known as \textit{Streptococcus agalactiae}, is a commensal gram-positive bacterium that resides in the gastrointestinal tract of some women. The gastrointestinal tract likely serves as a reservoir for genitourinary colonization, and colonization in women is largely asymptomatic and can be transient or persistent.\textsuperscript{17} Transmission from mother to infant occurs via ascending GBS infection into the uterine cavity after amniotic membrane rupture, where GBS may be aspirated by the fetus, or by exposure to GBS during passage through the vaginal canal.\textsuperscript{14} The vaginal-rectal colonization rates in pregnancy range from 10% to 30%.\textsuperscript{18-20} Around 50% of
infants born to colonized women who have not received antibiotics during labor are colonized with GBS, and around 1-2% of those infants develop GBS EOD.\textsuperscript{14,21,22}

Other key risk factors for GBS EOD include preterm labor (less than 37 weeks gestation), prolonged rupture of membranes (18 hours or longer), maternal fever (100.4°F / 38.0°C or higher), GBS bacteriuria at any point during the current pregnancy, and a maternal history of having a previous infant with GBS EOD.\textsuperscript{6}

\textbf{Intrapartum Antibiotic Prophylaxis}

Since the 1980s, intravenous intrapartum antibiotic prophylaxis (IAP) has been shown to greatly reduce the rate of GBS transmission and incidence of GBS EOD.\textsuperscript{14,21-23} IAP is thought to reduce the vertical transmission of GBS by reducing the burden of maternal GBS colonization during delivery, preventing intrapartum fetal colonization by GBS, and by treating the GBS that have successfully colonized or infected the fetus.\textsuperscript{21} The current cornerstone of GBS EOD prevention is GBS screening to identify appropriate candidates for IAP.

The antibiotic of choice for preventing GBS EOD is intravenous penicillin. Intravenous penicillin has a narrow spectrum of activity that covers gram-positive bacteria, including GBS, and can cross the placenta to reach the fetus.\textsuperscript{24} Ampicillin is an alternative first-line agent that is also highly effective against GBS and can cross the placenta, but has a broader spectrum of activity.\textsuperscript{6} Intravenous penicillin and ampicillin are around 89\% effective in preventing GBS EOD if given at least 4 hours before delivery.\textsuperscript{25}

For women with allergies to penicillin, different antibiotics are considered depending on the severity of the allergy. Patients with a history of angioedema, respiratory distress, urticaria, or anaphylaxis in response to penicillin or a cephalosporin are at high risk of anaphylaxis.\textsuperscript{26}
Treatment options for high risk patients include clindamycin and vancomycin. However, while there is little GBS resistance to penicillin or cephalosporins, clindamycin resistance has been estimated to be 20% or higher.\textsuperscript{11,27,28} For women with high risk penicillin allergies and a GBS strain that is resistant to clindamycin, vancomycin remains the only option for IAP.\textsuperscript{6} A large disadvantage in using clindamycin or vancomycin is that neither readily cross the placenta, thereby limiting their effectiveness in preventing GBS EOD.\textsuperscript{29} For patients with allergies to penicillin but who are at low risk for anaphylaxis, cefazolin is an appropriate treatment as there is little cross-reactivity with penicillin, and it has been shown to readily cross the placenta and reach levels above the GBS minimum inhibitory concentration in the fetal serum and amniotic fluid. There is also very little GBS resistance to cefazolin.\textsuperscript{30-33}

**GBS Screening Guidelines in the United States**

In collaboration with American College of Obstetricians and Gynecologists (ACOG), the American Academy of Pediatrics (AAP), and several other organizations, the CDC first published guidelines on the prevention of perinatal GBS infection in 1996. In those guidelines, the CDC recommended identifying women at increased risk of transmitting GBS to their newborns through either an antepartum culture based screen at 35-37 weeks of gestation or an intrapartum risk factor based screen.\textsuperscript{34} In 2002, the CDC updated its guidelines to recommend universal culture based antepartum screening at 35-37 weeks gestation based on a large retrospective cohort study that showed antepartum culture based screening was more effective than an intrapartum risk factor based approach for GBS disease prevention.\textsuperscript{35,36} In 2010, the CDC again reaffirmed antepartum culture based screening over an intrapartum risk factor based approach in its updated guidelines.\textsuperscript{37}
Following the implementation of guidelines to identify and give IAP to pregnant women who are at increased risk of transmitting GBS to their newborns, the incidence of GBS EOD has decreased from 1.8 to 0.23 cases per 1,000 live births from the 1990s to 2015 in the United States. Although there has been a more than 80% reduction in the incidence of GBS EOD disease, screening guidelines and IAP have not impacted the incidence of GBS LOD, which has remained constant at around 0.25-0.5 cases per 1,000 live births. The mechanism by which newborns acquire LOD is thought to be unrelated to intrapartum management.

GBS Screening Guidelines in Europe

While the United States adopted universal antepartum screening for GBS in 2002, there was a lack of such consensus among European countries. While some countries adopted universal antenatal screening, others preferred risk based strategies for determining which women should receive IAP. There were also some countries that did not issue clear screening and treatment guidelines for GBS EOD prevention. The lack of consensus reflects several potential areas of concern regarding universal antepartum screening. There are concerns that the increased cost of implementing universal screening and IAP would not actually decrease the incidence of GBS EOD in countries with a very low prevalence of documented GBS colonization. Additionally, in order to optimize the positive and negative predictive value, antepartum screening cultures must be performed within 5 weeks of delivery. In 2015, 10% of births in the United States were preterm (occurring while under 37 weeks gestation), 25% of births were early term (occurring at 37-38 weeks gestation), and 58% were full term (occurring at 39-40 weeks gestation). If patients undergo antepartum screening at 35-36 weeks gestation, a majority will not deliver until 4-5 weeks later. It is
estimated that 3.2% of patients will have negative screening cultures but be positively colonized at the time of delivery, and 2.5% of patients will be positive during screening and negative at delivery. Following the implementation of universal antepartum screening and prophylaxis of women with positive GBS screen, there has been a more than 80% reduction in the incidence of GBS EOD. However, of those cases of GBS EOD that still occur, around 50-80% now occur in infants born to women with a negative antepartum screen because they were not treated with IAP. Even for those patients whose intrapartum GBS carrier status is accurately predicted by an antepartum culture, the results are not always available at the time of delivery to guide management.

In 2015, a European consensus conference issued recommendations for universal GBS screening. While the consensus conference acknowledged that adoption of antepartum culture based screening has resulted in a great reduction in the incidence of GBS EOD, they ultimately recommended using rapid nucleic acid amplification tests (NAAT) to identify appropriate candidates for IAP. In making its recommendation, the consensus conference emphasized that any intrapartum NAAT based screening should be conducted with a test that has a sensitivity and specificity not inferior to 90-95% and 95-98%, respectively, has a short turnaround time (30-45 minutes), and be available around the clock.

One of the biggest advantages of intrapartum NAAT is eliminating the possibility of patients converting from being GBS negative during an antepartum screen to being GBS positive during delivery or vice versa by decreasing the test to treatment time. The intrapartum test also avoids the possibility of a patient undergoing an antepartum culture based screen and then being lost to follow up. Additionally, the Xpert™ GBS assay (Cepheid, Sunnyvale, CA, USA), a United States Food and Drug Administration approved NAAT, can result in 30-50 minutes and is
largely automated, requiring very little human labor. The assay could be available around the clock, potentially without needing dedicated laboratory facilities or personnel.\textsuperscript{45} Several European studies have also illustrated that intrapartum NAAT based GBS screening approaches are cost neutral or cost-effective compared to antepartum culture based screening.\textsuperscript{46-48}

However, while intrapartum NAAT can identify GBS carriers in less than an hour, there are still concerns that the test may result in an error, and any delays in administering IAP could mean worse neonatal outcomes, as IAP has been shown to be the most effective if administered at least 4 hours before delivery.\textsuperscript{25,45}

Moreover, there are concerns about the effectiveness of IAP in patients with penicillin allergies who undergo intrapartum NAAT testing. Given the high rate of clindamycin resistance in GBS strains, sensitivity testing must be performed before clindamycin can be used for IAP. NAAT currently cannot perform antibiotic sensitivity testing. As such, women with high risk penicillin allergies can only receive intravenous vancomycin for IAP if they undergo intrapartum NAAT based testing, and due to its poor penetration across the fetal-placental unit, data on its efficacy is limited.\textsuperscript{6,29}

Given the potential downsides of intrapartum NAAT based screening for GBS, the 2019 ACOG guidelines reaffirmed antepartum culture based screening as the cornerstone for GBS EOD prevention for the United States. In an effort to increase the negative predictive value from 80\% to 95\% for antepartum screening and further decreased the incidence of GBS EOD, the 2019 guidelines recommended antepartum screening starting at 36 weeks gestation, rather than the previously recommended 35 weeks.\textsuperscript{6,39}

However, although the United States GBS guidelines recommend culture based screening, there are some American facilities that are opting to perform NAAT instead. A 2016 laboratory
survey found that 18.7% of laboratories offered NAAT based GBS screening, with 7.3% offering antepartum NAAT, 4.1% offering intrapartum NAAT, and 3.4% offering both intrapartum and antepartum NAAT. Of the laboratories that offer intrapartum NAAT, 29% had turnaround times of under an hour while 50% had turnaround times of 1-2 hours.\

**Statement of Purpose**

The purpose of this study is to determine the most cost-effective method of screening for maternal GBS colonization in order to identify candidates for IAP, reduce vertical transmission of GBS, and prevent cases of GBS EOD in the United States given the new 2019 ACOG recommendation to perform antepartum screening at 36 weeks gestation instead of 35 weeks. Specifically, the study aims to:

1. Compare the cost-effectiveness of culture versus NAAT based antepartum screening for GBS.
2. Compare the cost-effectiveness of antepartum versus intrapartum screening for GBS.
METHODS

A decision tree was constructed from a societal perspective with TreeAge Pro Suite 2018 (Williamstown, MA). With probabilistic sampling, the model simulated parallel cohorts of 10,000 pregnant patients who underwent screening for and management of GBS by different strategies. The model incorporates downstream effects of the different screening methods on direct patient care, patient outcomes, and health care costs. We assessed outcomes for the pregnant patients in terms of costs, and we assessed outcomes for the newborns both in terms of cost and quality-adjusted life years (QALY), a utility metric accounting for both life expectancy and quality of life for patients in a specified health state. Institutional review board approval was not required for this study because it did not involve actual patients.

Model Structure

The model starts with a pregnant patient who undergoes GBS screening with four possible strategies: 1) an antepartum culture based approach at 36 weeks gestation, 2) an antepartum NAAT based approach at 36 weeks gestation, 3) an intrapartum NAAT based approach for all women, or 4) a combined antepartum and intrapartum approach where women with a high risk penicillin allergy undergo culture based screening at 36 weeks gestation and all other women undergo intrapartum NAAT based screening (combined antepartum and intrapartum strategy). We present a simplified flow chart of the model in Figure 1, with the complete model structure available from the authors.

Patients considered to have a high risk allergy to penicillin include those with a known history of urticaria, angioedema, respiratory distress or anaphylaxis in response to receiving a penicillin or cephalosporin. In the antepartum strategies, if a patient had a high risk penicillin
allergy and was found to be GBS positive, subsequent sensitivity cultures were performed to determine the appropriate antibiotic for IAP. Patients with high risk penicillin allergies who get sensitivity cultures received either clindamycin or vancomycin for IAP. In the NAAT based intrapartum strategy, if a patient had a high risk penicillin allergy and was found to be GBS positive, they received empiric vancomycin as IAP because intrapartum NAAT cannot currently inform sensitivities and there is a potentially high rate of clindamycin resistance in GBS. Patients with no or low risk allergies to penicillin with indications for IAP received penicillin or cefazolin, respectively.

For strategies that include antepartum screening, the rate of conversion of patients from GBS negative at 36 weeks to GBS positive during delivery (negative to positive conversion) as well as the rate of conversion of patients from GBS positive at 36 weeks to GBS negative during delivery (positive to negative conversion) were considered. Patients who were initially GBS positive at 36 weeks but who convert to GBS negative during delivery still received IAP, and patients who were initially GBS negative at 36 weeks but who convert to GBS positive during delivery did not receive IAP.

For strategies that included intrapartum NAAT screening, the possibilities of false positives and false negatives were considered. Patients with false positive intrapartum NAAT testing received IAP and patients with false negative NAAT testing did not receive IAP.

For the combined antepartum and intrapartum strategy, patients with high risk penicillin allergies first underwent antepartum culture testing at 36 weeks gestation. If the antepartum culture test results were positive for GBS, then the patient underwent subsequent sensitivity testing. If the initial culture result was negative for GBS, the patient did not undergo subsequent testing.
For patients who did not have culture or NAAT results available during delivery, risk factor based screening was used to determine which patients required IAP. Patients received IAP if they had any of the following intrapartum risk factors: preterm labor (less than 37 weeks gestation), prolonged rupture of membranes (18 hours or longer), maternal fever (100.4°F / 38.0°C or higher), GBS bacteriuria at any point during the current pregnancy, or a maternal history of having a previous infant with GBS EOD per 2019 ACOG guidelines.\(^6\)

For the model, we assumed that all women have singleton pregnancies and are expecting to labor. We also assumed that women without previous high risk penicillin allergy symptoms would not suffer a new-onset anaphylactic reaction in response to getting IAP given that new anaphylactic reactions during pregnancy are very rare.\(^5\) GBS LOD was not included in the model because IAP has not been shown to significantly reduce the rates of GBS LOD.\(^1\)
Figure 1. Simplified flow chart of decision tree model.
A Patients at high risk for anaphylaxis received clindamycin or vancomycin after sensitivity results. Patients with no allergies or low risk allergies to penicillin received penicillin or cefazolin, respectively.

B Outcomes for GBS EOD include healthy, mild disability, moderate disability, severe disability, and death.

C Risk factors include preterm labor (less than 37 weeks gestation), prolonged rupture of membranes (18 hours or longer), maternal fever (100.4°F / 38.0°C or higher), GBS bacteriuria at any point during the current pregnancy, and a maternal history of having a previous infant with GBS EOD.

D Patients at high risk for anaphylaxis received empiric vancomycin because no sensitivity results were available.
Clinical Parameters

All clinical parameters were derived from an English language search of PubMed for relevant publications and their reference lists. Based on the published literature, we assumed a GBS colonization prevalence of 25% in pregnant women and a 1.5% risk of an untreated, colonized mother having an infant with GBS EOD.\textsuperscript{6,37,52} Antepartum culture sensitivity of 90.3% and specificity of 95.9% at 36 weeks gestation was extracted from a 2019 prospective multicenter cohort study by Virranniemi et al.\textsuperscript{40} Antepartum NAAT sensitivity and specificity of 99.5% and 98.9%, respectively, were extracted from a 2014 study comparing three U.S. Food and Drug Administration approved antepartum GBS NAAT.\textsuperscript{53} Intrapartum NAAT sensitivity of 93.7%, intrapartum NAAT specificity of 97.6%, as well as a 4.87% risk of an intrapartum NAAT resulting in an error or otherwise not resulting were extracted from a 2018 meta-analysis by Feuerschuette et al.\textsuperscript{54} We assigned the risk of healthy neonate, mild disability, moderate disability, severe disability, and death following GBS EOD based on a 2017 cost-effectiveness analysis by Albright et al (Table 1).\textsuperscript{52}

Given that this study aims to specifically examine the cost-effectiveness of different methods of screening for GBS under the 2019 ACOG recommendations to screen at 36 weeks gestation instead of 35 weeks, we used 1-positive predictive value (PPV) and 1-negative predictive value (NPV) of antepartum culture testing at 36 weeks to approximate the baseline positive to negative and negative to positive conversion rates, respectively. The PPV and NPV of 89.8 and 96.1, respectively, were extracted from the study by Virranniemi et al.\textsuperscript{40}

When modeling the effectiveness of IAP at preventing GBS EOD, we took into account the duration of IAP (whether fewer than 2 hours, greater than or equal to 2 hours but fewer than 4 hours, or greater than or equal to 4 hours), along with the type of antibiotic given. For patients
without high risk penicillin allergies, IAP was considered to be 67.57% effective if IAP was given for greater than or equal to 2 hours but fewer than 4 hours, based on estimates from Fairlie et al. and Lin et al. For patients without high risk penicillin allergies, IAP was assumed to be 89% effective if IAP was given 4 or more hours before delivery. For patients who had high risk penicillin allergies, the effectiveness of clindamycin was used to calculate IAP effectiveness when patients received clindamycin or vancomycin since there are no available studies that report on the effectiveness of intravenous vancomycin in preventing GBS EOD. Moreover, 31% of GBS strains were considered resistant to clindamycin. In cases where sensitivity cultures were not performed, clindamycin was considered 22% effective; however, if patients underwent sensitivity testing, the patients’ GBS strains were assumed to not be resistant to clindamycin, and clindamycin was considered 32% effective.

In cases where culture or NAAT results are unavailable during delivery, patients underwent a risk factor based approach for GBS EOD prevention. In a large retrospective cohort study, Schrag et al. reported a relative risk of 0.48 for GBS disease when comparing women who underwent antepartum culture based screening to those who underwent a risk factor based approach. The value of 1/0.48 was used to assign a probability of developing GBS EOD for patients whose antepartum culture results were unavailable. That probability was subsequently applied to all screening methods where patients underwent a risk factor based approach, for example when intrapartum NAAT resulted in an error and patients underwent risk factor based screening.
<table>
<thead>
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<th>Variable</th>
<th>Mean Value</th>
<th>Distribution (if applicable)</th>
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</table>
Costs

The costs of antibiotics, screening and sensitivity cultures, and antepartum NAAT screening were sourced from National Medicare reimbursement rates and given a gamma distribution to allow for a wider range. The cost of intrapartum NAAT was estimated based on costs reported in the literature in United States dollars (USD) and varied widely in sensitivity analysis. The costs associated with mild disability, moderate disability, severe disability and neonatal death as a result of GBS EOD were extracted from Albright et al. The model takes into account the cost of testing, treatment, follow-up, and lifetime medical expenses of the neonate.

When incorporating costs into the model, we assumed patients receiving IAP received IAP per the ACOG 2019 recommended dosages: penicillin G 5 million units as a loading dose, then 3 million units every 4 hours until delivery; cefazolin 2 g loading dose, then 1 g every 8 hours until delivery; clindamycin 900 mg every 8 hours until delivery; vancomycin 20 mg/kg every 8 hours. We assigned costs for 4 hours of IAP for patients receiving IAP as patients were considered adequately treated after 4 hours. All costs were inflation adjusted to 2019 USD (Table 2).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean Value</th>
<th>Distribution (if applicable)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBS culture</td>
<td>18.78</td>
<td>Gamma (100, 5.32)</td>
<td>Medicare reimbursement</td>
</tr>
<tr>
<td>GBS culture and sensitivity</td>
<td>26.29</td>
<td>Gamma (100, 3.80)</td>
<td>Medicare reimbursement</td>
</tr>
<tr>
<td>Antepartum NAAT</td>
<td>38.99</td>
<td>Gamma (99.95, 2.56)</td>
<td></td>
</tr>
<tr>
<td>Intrapartum NAAT</td>
<td>64.02</td>
<td>Triangular (38.03, 90)</td>
<td></td>
</tr>
<tr>
<td>Penicillin 5 million and 2.5 million units</td>
<td>29.82</td>
<td>Gamma (100, 3.35)</td>
<td>Medicare reimbursement</td>
</tr>
<tr>
<td>Cefazolin 2 g dose</td>
<td>3.00</td>
<td>Gamma (100, 16.62)</td>
<td>Medicare reimbursement</td>
</tr>
<tr>
<td>Clindamycin 900 mg</td>
<td>9.90</td>
<td>Gamma (100, 5.05)</td>
<td>Medicare reimbursement</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>14.59</td>
<td>Gamma (100, 3.43)</td>
<td>Medicare reimbursement</td>
</tr>
<tr>
<td>Hospital cost of GBS EOD</td>
<td>20,322.38</td>
<td>Triangular (2,462.22, 46,271.60)</td>
<td></td>
</tr>
<tr>
<td>Lifetime cost of GBS EOD if mild disability</td>
<td>70,229.79</td>
<td>Triangular (0, 122,492.03)</td>
<td></td>
</tr>
<tr>
<td>Lifetime cost of GBS</td>
<td>122,492.03</td>
<td>Triangular (70,229.79, 122,492.03)</td>
<td></td>
</tr>
<tr>
<td>Description</td>
<td>Cost</td>
<td>Distribution</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>------------</td>
<td>-----------------------</td>
<td></td>
</tr>
<tr>
<td>EOD if moderate disability</td>
<td>284,433.31</td>
<td>Triangular (89,717.18, 739,653.07)</td>
<td></td>
</tr>
<tr>
<td>Lifetime cost of GBS EOD if severe disability</td>
<td>284,433.31</td>
<td>Triangular (89,717.18, 739,653.07)</td>
<td></td>
</tr>
<tr>
<td>Cost of GBS EOD if neonatal death</td>
<td>97,553.67</td>
<td>Triangular (73,314.41, 138,505.24)</td>
<td></td>
</tr>
</tbody>
</table>

A All costs are in 2019 USD.

B CPT code: 87081, 87077, 87140, 87143, 87147, and 87149.

C CPT code: 87181, 87184, and 87186.

D CPT code: 87653.

E The cost for vancomycin was calculated for a 90 kg adult (based on the average weight of 77.3 kg for non-pregnant women over 20 years old in the United States and the recommended weight gain in pregnancy). 60,61
Outcomes

The utilities of different GBS EOD disease states were measured in QALY over the span of a patient’s lifetime (Table 3). The utilities associated with different GBS EOD disease states were extracted from Albright et al.\textsuperscript{52} The model does not include prolonged neonatal hospital course as a disutility or take into account productivity losses from disability.

Table 3. List of Utilities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean Value\textsuperscript{A}</th>
<th>Distribution (if applicable)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Neonate</td>
<td>30.11 QALY</td>
<td>Triangular (19.58, 79)</td>
<td>\textsuperscript{52}</td>
</tr>
<tr>
<td>Mild disability</td>
<td>26.80 QALY</td>
<td>Triangular (17.42, 70.31)</td>
<td>\textsuperscript{52}</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>19.92 QALY</td>
<td>Triangular (13.30, 46.92)</td>
<td>\textsuperscript{52}</td>
</tr>
<tr>
<td>Severe disability</td>
<td>8.58 QALY</td>
<td>Triangular (6.90, 12.48)</td>
<td>\textsuperscript{52}</td>
</tr>
</tbody>
</table>

\textsuperscript{A} QALY, quality-adjusted life years.
Statistical Analysis

The two primary measures used in this study were incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB). The former is defined as

\[
\frac{\text{Cost of Strategy 1} - \text{Cost of reference strategy}}{\text{Expected utility of strategy 1} - \text{Expected utility of reference strategy}}.
\]

The ICER was assessed using the recommended willingness-to-pay (WTP) threshold in the U.S. of $100,000/QALY. ICER was used in base case calculation and probabilistic sensitivity analysis. The other indicator was net monetary benefit (NMB), defined as \( \text{expected utility} \times \text{WTP} - \text{cost} \), and it was used to compare strategies in sensitivity analyses. If strategy 1 has a higher NMB than strategy 2, it is more cost-effective by the ICER ratio.

Base case calculations were performed using the mean values for each variable. One- and two-way sensitivity analyses varying key variables, probabilistic sensitivity analysis simulating a cohort of 10,000 patients were performed to assess the robustness of the final conclusion. Cost-effectiveness acceptability curves were generated in order to reflect the uncertainly in cost-effectiveness calculations. All statistical analyses using TreeAge were performed by Xiao Wu.

Validation

Face validation was performed to review problem formulation, data source, model structure, and results. Internal validation was performed with TreeAge software. External validation was performed by comparing our results with previous cost-effectiveness analyses. A calibration validation is not applicable because of the lack of randomized control trials comparing antepartum culture based screening and intrapartum NAAT based screening.
RESULTS

**Base Case Calculation**

Base case calculation was performed using the mean value for each variable. Antepartum culture based screening at 36 weeks yielded the lowest cost, but the intrapartum NAAT based screen and the combined antepartum and intrapartum screen were more effective. The ICER is $97,791.02/QALY and $92,109.56/QALY with reference to antepartum culture based screen, respectively, which are both below the WTP threshold in the U.S. of $100,000/QALY.\(^6\) The ICER of intrapartum NAAT based screen was negative with reference to combined antepartum and intrapartum screen. Thus, overall, the most effective strategy is the combined antepartum and intrapartum screen (Table 2).

<table>
<thead>
<tr>
<th></th>
<th>Cost A</th>
<th>Effectiveness (QALY) B</th>
<th>ICER ($/QALY) C</th>
</tr>
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<tbody>
<tr>
<td>Antepartum culture based screen</td>
<td>152.80</td>
<td>42.886194</td>
<td>Reference</td>
</tr>
<tr>
<td>Antepartum NAAT based screen</td>
<td>173.32</td>
<td>42.886157</td>
<td>Negative</td>
</tr>
<tr>
<td>Combined antepartum and</td>
<td>191.22</td>
<td>42.886611</td>
<td>92109.56</td>
</tr>
<tr>
<td>intrapartum screen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrapartum NAAT based screen</td>
<td>192.96</td>
<td>42.886605</td>
<td>97791.02</td>
</tr>
</tbody>
</table>

\(^A\) Costs are in 2019 USD.

\(^B\) QALY, quality-adjusted life years.

\(^C\) ICER, incremental cost-effectiveness ratio.
Probabilistic Sensitivity Analysis

We performed probabilistic sensitivity analysis to simulate a cohort of 10,000 patients drawing input parameters from their respective distributions. When comparing antepartum culture based screening at 36 weeks to the combined antepartum and intrapartum screen (the two nondominated strategies in the base case), the combined antepartum and intrapartum approach is the more cost-effective strategy in 49% of the iterations (Figure 2).

Sensitivity Analyses

One-Way Sensitivities

We performed a one-way sensitivity analysis varying the prevalence of GBS over a wide range (0-50%) while keeping all other variables fixed. The results demonstrated that intrapartum NAAT screening was the most favorable strategy for a GBS prevalence below 18%. Between 18% and 22%, the combined intrapartum and antepartum approach was the most favorable strategy. Between 22% and 26%, the antepartum culture was the optimal strategy. Above 26%, antepartum NAAT is the optimal screening strategy (Figure 3).

We also varied the cost of an intrapartum NAAT from 0 to 300 USD while keeping all other variables fixed. We found that the combined approach is the best strategy below 67 USD. Above a cost of 67 USD, the antepartum culture based screen becomes a more optimal approach than the combined approach and the intrapartum NAAT (Figure 4).

Similarly, we varied the percentage of people who had high risk penicillin allergies from 0 to 50% and found that the combined antepartum and intrapartum approach remained the most optimal strategy throughout the entire range (Figure 5).
We also varied the effectiveness of clindamycin (without sensitivity testing) between 0 and 60% and found that the combined approach was the optimal strategy for an effectiveness of higher than 7%, but intrapartum NAAT was the best strategy for a clindamycin effectiveness lower than 7% (Figure 6).

We varied the effectiveness of receiving at least two hours but less than 4 hours of penicillin from 0-100% and found that at an effectiveness of 70%, antepartum culture screening becomes the optimal strategy over the combined approach and the intrapartum NAAT. At an effectiveness of less than 70%, the combined approach is the optimal strategy (Figure 7).

We also examined the negative to positive GBS conversion rate for patients undergoing antepartum screening and found that at a conversion rate of below 3.8%, the antepartum approaches are more cost-effective than the intrapartum NAAT and the combined approach. At a negative to positive conversion rate of above 3.8%, the intrapartum and combined approaches are more favorable strategies (Figure 8). At 36 weeks gestation, the negative to positive conversion rate is estimated to be 3.9%.40

Additionally, we varied the risk of an intrapartum NAAT resulting in an error from 0-50% and found that at around an error rate of 5%, the combined approach and the intrapartum NAAT become less cost-effective than the antepartum culture (Figure 9).
Two-Way Sensitivities

A two-way sensitivity analysis was done varying both the negative to positive (0-50%) and positive to negative (0-50%) GBS conversion rate. The results (Figure 10) showed that for a negative to positive conversion rate of more than 13%, intrapartum NAAT screening was the most optimal approach regardless of the positive to negative conversion rate. For a negative to positive conversion rate of less than 3%, antepartum culture based screening was the most optimal strategy regardless of the positive to negative conversion rate.

Additionally, a two-way sensitivity analysis was performed comparing the negative to positive conversion rate (0-50%) and the effectiveness of clindamycin (0-60%). The results (Figure 11) showed that intrapartum NAAT was the most optimal strategy for a negative to positive conversion rate of at least 7.5% regardless of the effectiveness of clindamycin. Antepartum culture based screening was the most optimal strategy for a negative to positive conversion rate of less than 2.5%, regardless of the effectiveness of clindamycin.

Similarly, a two-way sensitivity analysis was performed comparing the negative to positive conversion rate (0-50%) and the effectiveness of at least 2 hours but fewer than 4 hours of penicillin (0-100%). The results were similar to the two-way sensitivity comparing the negative to positive conversion rate and the effectiveness of clindamycin. Above a negative to positive conversion rate of 5%, intrapartum NAAT was the most optimal approach regardless of the effectiveness of penicillin. Below a negative to positive conversion rate of 3%, antepartum culture based screening is the best strategy (Figure 12).

The effectiveness of at least 2 hours but fewer than 4 hours of penicillin (0-100%) and effectiveness of clindamycin (0-60%) were also compared. At a penicillin effectiveness of higher than around 70%, antepartum culture based screening was the most optimal strategy regardless
of the effectiveness of clindamycin. Below a penicillin effectiveness of 70%, the combined strategy was the optimal approach if clindamycin effectiveness was higher than 7%, and the intrapartum NAAT approach was the optimal strategy if the clindamycin effectiveness was less than 7% (Figure 13).
**Cost-effectiveness Acceptability Curves**

We generated cost-effectiveness acceptability curves comparing intrapartum NAAT and antepartum culture. Intrapartum NAAT had a 0.48 probability of being cost-effective over antepartum culture at a WTP of $100,000/QALY (Figure 14). At a WTP of $110,000/QALY, intrapartum NAAT had a 0.50 probability of being cost-effective over antepartum culture. At WTP thresholds of higher than $110,000/QALY, intrapartum NAAT had a higher than 0.50 probability of being cost-effective over antepartum culture.

We also generated cost-effectiveness acceptability curves comparing antepartum NAAT and antepartum culture. Antepartum NAAT had a 0.25 probability of being cost-effective over antepartum culture at a WTP of $100,000/QALY. At all WTP thresholds between $0/QALY and $200,000/QALY, antepartum NAAT had a less than 0.50 probability of being cost-effective over antepartum culture (Figure 15).

When comparing the combined approach and antepartum culture using cost-effectiveness acceptability curves, the combined approach had a 0.48 probability of being cost-effective over antepartum culture at a WTP of $100,000/QALY (Figure 16). At a WTP of $110,000/QALY, the combined approach had a 0.50 probability of being cost-effective over antepartum culture. At WTP thresholds of higher than $110,000/QALY, the combined approach had a higher than 0.50 probability of being cost-effective over antepartum culture.
Discussion

Our results indicate that intrapartum screening for GBS could be cost-effective compared to antepartum screening. Specifically, intrapartum NAAT based screening and a combined antepartum and intrapartum approach (where women who are known to have high risk allergies to penicillin undergo culture based screening at 36 weeks gestation and all other patients undergo intrapartum NAAT based screening) are cost-effective interventions compared to antepartum screening with culture or NAAT in the base case. While antepartum culture had the lowest cost in the base case, the combined approach and the intrapartum NAAT had an ICER of $92,109.56/QALY and $97,791.02/QALY with reference to antepartum culture based screen, respectively, both of which are lower than the ICER threshold of $100,000/QALY that is considered to be cost-effective in the United States. The results of our analysis are similar to ones in Europe that have found intrapartum NAAT to be a cost neutral or cost-effective way to screen for and reduce GBS disease.

The higher effectiveness of the intrapartum and combined approaches compared to antepartum approaches is primarily driven by the negative to positive GBS conversion rate. This conversion rate is a major disadvantage of antepartum screening. Van Dyke et al. found in a large, retrospective cohort study that 61.4% of term infants with GBS disease had mothers who had tested negative for GBS on an antepartum screen. We found that antepartum approaches were only cost-effective if the negative to positive conversion rate was below 3.8%. While there are large ranges reported for the NPV of antepartum screening in general, Virranniemi et al. found that the negative to positive conversion rate at 4 weeks before delivery was 3.9%. Given the large impact of the negative to positive conversion rate on which screening method is most cost-effective, further studies need to be done to determine the actual GBS conversion rate of
women who are screened at 36 weeks in order to determine if screening at 36 weeks gestation instead of 35 weeks potentially decreases the negative to positive conversion rate to below 3.8%.

One potential explanation for the discrepant American and European approaches to screening for GBS could be the difference in GBS prevalence. While the reported prevalence of GBS colonization in the United States is around 25%, some European countries report a much lower prevalence. Our analyses showed that when GBS prevalence was lower than around 22%, intrapartum approaches were more favorable than antepartum ones. Antepartum approaches became more favorable as GBS prevalence increased.

One reason the 2019 ACOG guidelines do not recommend intrapartum NAAT based screening for GBS is concern that a high proportion of intrapartum NAAT could result in error or otherwise fail to result. In our base case, the error rate was assigned to be 4.87% based on data from a 2018 meta-analysis of intrapartum NAAT performance. Our analysis found that intrapartum approaches become less cost-effective than an antepartum culture at intrapartum NAAT error rates of 5% or higher. While there are some reports of up to 10% of intrapartum NAAT resulting in an error or otherwise not resulting, there are also cases where initially high error rates can be decreased greatly after appropriate training on proper usage of the intrapartum NAAT machine. Thus, any attempt to enact intrapartum NAAT based screening should include provisions to properly train testing staff in order to minimize the error rate.

Additionally, the 2019 ACOG guidelines recommend that women receive at least 4 hours of IAP for optimal GBS EOD prevention. Even in cases when intrapartum NAAT does result without an error, there is still concern that the delay in initiating IAP in order to perform an intrapartum NAAT could translate to a higher risk of GBS EOD as more laboring women might deliver before receiving an adequate duration of IAP. In 2012, El Helali et al. reported that 55%
of patients received at least two doses of IAP before delivery under antepartum culture based screening, compared to 50% when their institution converted to intrapartum NAAT based screening.\textsuperscript{46} In our base case analysis, we assumed IAP had a 67.57% efficacy if the duration of treatment was for at least 2 hours but fewer than 4 hours. Under those assumptions, the intrapartum approaches were more cost-effective than the antepartum culture even though a smaller proportion of patients received an optimal duration of IAP. However, we found that when the effectiveness of receiving at least 2 but fewer than 4 hours of IAP was 70% or higher, antepartum culture based screening became the most effective strategy. Together, these results suggest that the delay in administering IAP in order to perform intrapartum NAAT screening could potentially lead to worse outcomes, as there are some studies that support a high efficacy of receiving between 2 and 4 hours of IAP.\textsuperscript{55,65-67}

Another reason that the 2019 ACOG guidelines do not recommend intrapartum NAAT screening is the lack of information on sensitivities for patients who have high risk allergies to penicillin. While there is little resistance to penicillin, ampicillin, and cefazolin in GBS, GBS does show significant resistance to clindamycin.\textsuperscript{30} However, a combined antepartum and intrapartum approach would avoid this concern as patients with known penicillin allergies could get sensitivity cultures antepartum, if necessary. The majority of patients, those without penicillin allergies, could be screened intrapartum and avoid the possibility of negative to positive GBS conversion between testing and delivery. When we varied the percentage of people with high risk penicillin allergies, the combined approach was the most cost-effective approach for the entire range.
Limitations

Our study has several limitations. First, it is very difficult to estimate the cost of performing an intrapartum NAAT around the clock in the United States. Haberland et al. estimates the cost of intrapartum NAAT to be $26 in 2001 USD.\textsuperscript{58} This estimate takes into account the base cost of the NAAT machine (divided per test), as well as the supplies to run individual tests and the time for a technician to run the test. However, the estimate assumes the presence of an on-site laboratory that would be available around the clock. Moreover, the base cost of the machine could be exorbitantly high if distributed per test for institutions without very high obstetrical volumes. Moreover, performing intrapartum NAAT would require a dedicated space for the machine, potentially on the labor unit for the quickest turnaround time. Notably, while some laboratories in the United States have started offering intrapartum NAAT for GBS screening, only 29\% had turnaround times of under an hour.\textsuperscript{49} While intrapartum NAAT could yield GBS carrier results in under an hour under ideal circumstances, this fast turnaround may only be possible with a large amount of structural investment and support staff. Particularly for institutions with high obstetric volumes, there would likely need to be an increase in staff in order to perform individual intrapartum NAAT around the clock. There is a paucity of literature reporting the actual cost of performing an intrapartum NAAT in the United States and that is a large limitation to this study. Based on the best available literature, intrapartum NAAT was assigned a cost of 64.02 USD in our base case analysis; however, our analyses showed that antepartum culture based screen becomes a more optimal approach than the intrapartum NAAT or combined approaches at an intrapartum NAAT cost of around 67 USD. While we were able to vary the cost of intrapartum NAAT across a wide range in our sensitivity analysis, additional data is needed to more accurately reflect the infrastructural and staffing cost associated with
intrapartum NAAT, particularly since the model is so sensitive to the cost of intrapartum NAAT. In the event that our base case underestimates the infrastructural cost of implementing intrapartum NAAT, antepartum culture based screening could be the optimal strategy for preventing GBS EOD in the United States.

Another limitation in our study is the conflicting data surrounding the effectiveness of different durations of IAP. While Fairlie et al. did not find a statistically significant difference in effectiveness when comparing IAP of fewer than 4 hours to no IAP, Lin et al. found that IAP administered at least 2 hours before delivery was 89% effective in reducing the incidence of GBS EOD. Additionally, there are some studies that report a significant reduction in colony counts after 2 hours of IAP. However, ACOG still recommends that women receive at least 4 hours of IAP for optimal GBS EOD prevention. For base case calculations, we assigned the effectiveness of receiving at least 2 hours but fewer than 4 hours of IAP to be 67.57% based on a combination of estimates from both Fairlie et al. and Lin et al. When we varied the effectiveness of receiving at least 2 but fewer than 4 hours of IAP, our analyses showed that at an effectiveness of 70%, antepartum culture screening becomes the optimal strategy over an intrapartum approach. Further studies are needed to verify the actual effectiveness of receiving fewer than 4 hours of IAP, as this metric has a large impact on determining the most cost-effective approach to GBS screening.

Additionally, we assumed that the effectiveness of cefazolin was the same as penicillin. While there are no specific studies reporting cefazolin effectiveness against GBS EOD, cefazolin acts similarly to penicillin, has been shown to cross the placenta, and has little resistance among GBS strains. We also assigned the effectiveness of clindamycin to individuals receiving vancomycin, since there is no literature on the effectiveness of vancomycin in preventing GBS
EOD. There is little reported vancomycin resistance among GBS strains, so the effectiveness of vancomycin could potentially be underestimated. However, our sensitivity analysis shows that intrapartum and combined approaches were more cost-effective than antepartum approach across a wide range of clindamycin/vancomycin effectiveness and the combined approach was the optimal strategy for an effectiveness of higher than 7%.

Our study is also limited by the assumption that all deliveries are of singleton babies. Moreover, our costs also do not account for indirect costs, meaning the actual cost of GBS EOD is likely to be higher than estimated.

Finally, results of cost-effectiveness analyses are inherently associated with uncertainty, as these analyses are performed using cost and effectiveness estimates for different interventions. Although we have attempted to use the best available data from published literature for our estimates, there are some variables that require further investigation for more accurate cost-effectiveness modeling. We performed various sensitivity analyses and generated different cost-effectiveness acceptability curves in order to reflect the uncertainty associated with this study.
Conclusion

A combined antepartum and intrapartum screening approach was the optimal strategy in our base analysis. We found that intrapartum screening methods involving NAAT could potentially be cost-effective interventions to reduce the morbidity and mortality of GBS disease, particularly when GBS prevalence is below 22%, there is a negative to positive conversion rate of above 3.8%, and when intrapartum NAAT error rates are below 5%. However, antepartum culture based screening is more favorable when the cost of intrapartum NAAT is above 67 USD, the efficacy of receiving more than 2 but fewer than 4 hours of IAP is above 70%, and the intrapartum NAAT error rates are above 5%.
Figure 2. Incremental Cost-effectiveness for Combined Antepartum and Intrapartum Screen vs Antepartum Culture Based Screen. Scatter plot of Monte Carlo simulation illustrating that the combined antepartum and intrapartum screen is more cost-effective than the antepartum culture based screen in 49% of cases. The dashed line indicates a willingness-to-pay (WTP) threshold of $100,000/QALY. Points to the right of the dashed line indicate a higher incremental effectiveness.
Figure 3. One-way Sensitivity Analysis Varying the Prevalence of GBS. A higher net monetary benefit is more favorable.
Figure 4. One-way Sensitivity Analysis Varying the Cost of Intrapartum NAAT. A higher net monetary benefit is more favorable.
Figure 5. One-way Sensitivity Analysis Varying the Rates of High Risk Penicillin Allergies.

A higher net monetary benefit is more favorable.
Figure 6. One-way Sensitivity Analysis Varying the Effectiveness of Clindamycin. The clindamycin effectiveness values reported reflect effectiveness before any sensitivity testing is conducted. Clindamycin effectiveness was also applied to patients receiving vancomycin. A higher net monetary benefit is more favorable.
Figure 7. One-way Sensitivity Analysis Varying the Effectiveness of Receiving ≥2 but <4 Hours of Penicillin IAP. A higher net monetary benefit is more favorable.
Figure 8. One-way Sensitivity Analysis Varying the Negative to Positive GBS Conversion Rate. A higher net monetary benefit is more favorable.
Figure 9. One-way Sensitivity Analysis Varying the Intrapartum NAAT Error Rate. A higher net monetary benefit is more favorable.
Figure 10. Two-way Sensitivity Analysis Varying the Negative to Positive and Positive to Negative GBS Conversion Rate. The color in each region represents the area in which the corresponding strategy is more cost-effective.
Figure 11. Two-way Sensitivity Analysis Varying the Negative to Positive GBS Conversion Rate and the Effectiveness of Clindamycin. The clindamycin effectiveness values reported reflect effectiveness before any sensitivity testing is conducted. Clindamycin effectiveness was also applied to patients receiving vancomycin. The color in each region represents the area in which the corresponding strategy is more cost-effective.
Figure 12. Two-way Sensitivity Analysis Varying the Negative to Positive GBS Conversion Rate and the Effectiveness of Receiving ≥2 but <4 Hours of Penicillin IAP. The color in each region represents the area in which the corresponding strategy is more cost-effective.
Figure 13. Two-way Sensitivity Analysis Varying the Effectiveness of Clindamycin and the Effectiveness of Receiving ≥2 but <4 Hours of Penicillin IAP. The clindamycin effectiveness values reported reflect effectiveness before any sensitivity testing is conducted. Clindamycin effectiveness was also applied to patients receiving vancomycin. The color in each region represents the area in which the corresponding strategy is more cost-effective.
Figure 14. Cost-effectiveness Acceptability Curve Comparing Intrapartum NAAT and Antepartum Culture Approaches. The y axis reflects the probability that a particular strategy is cost-effective over the other.
Figure 15. Cost-effectiveness Acceptability Curve Comparing Antepartum NAAT and Antepartum Culture Approaches. The y axis reflects the probability that a particular strategy is cost-effective over the other.
Figure 16. Cost-effectiveness Acceptability Curve Comparing Combined and Antepartum Culture Approaches. The y axis reflects the probability that a particular strategy is cost-effective over the other.
REFERENCES