MAJOR ARTICLE

Multicenter Study of a Rapid Molecular-Based Assay for the Diagnosis of Group B *Streptococcus* Colonization in Pregnant Women

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(See the editorial commentary by Schrag on pages 1136–8)

Background. Current prevention of infection due to group B *Streptococcus* (GBS) involves giving intrapartum antibiotics to women on the basis of either antenatal culture colonization status or presence of risk factors.

Methods. We prospectively compared the performance characteristics of a rapid molecular diagnostic test (IDI-Strep B; Infectio Diagnostic) with culture for intrapartum GBS detection after 36 weeks' gestation in 5 North American centers during the period September 2001–May 2002. Antenatal GBS screening was done according to the usual practice of participating hospitals. Two combined vaginal/anal specimens were obtained from participants during labor by use of standard techniques and processed by the same laboratories that processed the antenatal specimens. Each swab sample was processed simultaneously by culture and with IDI-Strep B. The collected specimens were randomized for order of testing of the swab samples by culture or the rapid test.

Results. Of enrolled women, 803 (91.1%) were eligible for analysis. The overall intrapartum GBS colonization rate by culture was 18.6% (range, 9.1%–28.7%). Compared with intrapartum culture, the molecular test had a sensitivity of 94.0% (range, 90.1%–97.8%), specificity of 95.9% (range, 94.3%–97.4%), positive predictive value of 83.8% (range, 78.2%–89.4%), and negative predictive value of 98.6% (range, 97.7%–99.5%). The molecular test was superior to antenatal cultures (sensitivity, 94% vs. 54%; $P < .0001$) and prediction of intrapartum status on the basis of risk factors (sensitivity, 94% vs. 42%; $P < .0001$).

Conclusion. Use of this test for determination of GBS colonization during labor is highly sensitive and specific and may lead to a further reduction in rates of neonatal GBS disease.

Group B *Streptococcus* (GBS) is the leading cause of infectious morbidity and mortality among newborns in North America [1–5]. The prevalence of GBS colonization in pregnant women varies from 15%–40% [6–8], with an incidence of 0.6 cases of early-onset neonatal disease per 1000 live births in the United States in 2000 [1]. Two approaches to the identification and prevention of GBS colonization were previously recommended by the Centers for Disease Control and Prevention (CDC) [9]. The first approach (i.e., the screening-based approach) consisted of screening pregnant women for GBS at 35–37 weeks of gestation by culturing vaginal/anal swab samples in a selective broth medium and administering intrapartum penicillin or ampicillin to all colonized women or those delivering preterm [9]. The second approach (i.e., the risk-based approach) consisted of administration of antibiotic prophylaxis on the basis of known risk factors [9]. In the 2002 revised guidelines, the screening approach was recommended as the first-line approach, with the risk-based approach suggested for use as backup in specific situations [10]. Although current preventive methods have been very effective [1, 2, 4], the culture method has the following limitations: it requires ⩾36 h, it has a predictive value

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for GBS colonization at delivery of between 69% [11] and 87% [12], screening results are not always known to the physician at the time of delivery, and some women do not undergo screening [10, 13]. Thus, some women may not be appropriately treated for GBS colonization or may be unnecessarily treated with antibiotics.

A sensitive rapid-screening test that could accurately detect women carrying GBS during labor could obviate the need for prenatal screening while reducing the risk associated with antibiotic prophylaxis for noncolonized women. Previous commercially available tests have lacked sensitivity and specificity, compared with the standard broth culture test [14–19]. In-house GBS-specific PCR-based assays have demonstrated better sensitivity but require complicated procedures that are not easily implemented in clinical laboratories [20–22].

IDI-Strep B (Infectio Diagnostic) is a qualitative in vitro diagnostic test for rapid detection of GBS in vaginal/anal specimens from maternity patients. The test uses a PCR assay to amplify GBS-specific DNA and a fluorogenic probe to detect the amplified GBS target. The test is performed on the SmartCycler (Cepheid) automated analyzer. In a single-site investigational trial, the selected primers and probe yielded a sensitivity of 97.0% (32 of 33 samples had results that were confirmed by culture), a specificity of 100%, a negative predictive value (NPV) of 98.8%, and a positive predictive value (PPV) of 100% for detecting GBS compared with culture results [23].

The present multisite prospective investigational study was undertaken to establish the analytical performance of IDI-Strep B in determining intrapartum GBS colonization of women under diverse clinical conditions.

METHODS

Sample size calculation. The study sample size was determined to achieve performance characteristics with 95% CIs within 4% with a 90% power [24]. We assumed an average GBS prevalence of 20% for the population to be tested [6–8]. For a test sensitivity (or specificity) of 95%, compared with intrapartum culture, 114 GBS-positive women or a total of 570 women were needed, whereas for a test sensitivity (or specificity) of 90%, 216 GBS-positive women or a total of 1080 women were needed.

Study design. The research ethics committees of all the participating institutions approved the study. From 22 February through 31 May 2002, eligible pregnant women who presented to the hospital in labor after 36 weeks' gestation and who met the inclusion criteria were enrolled. Women were eligible if they had no contraindication to a vaginal examination (e.g., bleeding), had not used a systemic or topical (vaginal) antibiotic treatment in the week prior to admission, did not have placenta previa, and did not have an urgent indication to proceed to delivery.

Collection of specimens. A pair of combined vaginal and anal specimens was collected from participants by use of the Copan Venturi Transystem (Copan Diagnostics) collection device, consisting of a rayon swab and liquid Stuart transport medium. Excessive secretions from the vagina were wiped away prior to sampling secretions from the lower one-third of the vagina. The same swab was then inserted ~2.5 cm beyond the anal sphincter, and gently rotated to sample anal crypts. All swabs were placed back into their protective sleeves, which contained transport medium. All specimens were collected prior to initiation of intrapartum antibiotic prophylaxis for GBS colonization. At the time of specimen collection, information on the presence of potentially interfering substances or those substances associated with membrane rupture (e.g., meconium, amniotic fluid, or blood) in the specimen was recorded. Specimens were kept at room temperature for a maximum of 24 h before batch testing. The specimens were numbered with preprinted labels such that the order of testing for consecutive specimens was reversed to ensure that each swab (first or second collected) was used approximately as many times for culture as for IDI-Strep B. The culture and the IDI-Strep B were performed by different individuals, and the individual performing each test was blinded to the result of the other test.

Culture methods. All antenatal specimens and 1 of each pair of intrapartum swab samples of the distal vagina and anorectum were inoculated into either 1 of 2 selective broth media (both approved by the US Food and Drug Administration and recommended by the CDC for routine clinical use): Todd-Hewitt broth (Difco Laboratories), supplemented with gentamicin (8 μg/mL) and nalidixic acid (15 μg/mL), or Lim Broth (Todd-Hewitt broth with 15 μg/mL nalidixic acid and 10 μg/mL colistin; PML Microbiologicals or BBL). Inoculation was followed by overnight incubation and subculturing to 5% sheep blood agar for 18–24 h at 35°C with 5% CO_2. Specific identification of colonies suggestive of GBS was done with a commercial slide agglutination kit (PathoDx; Diagnostic Products). If GBS was not identified after incubation for 18–24 h on a sheep blood agar plate, the plate was reincubated and reexamined at 48 h.

Principle of the IDI-Strep B assay. The PCR master mixture contained all reagents necessary for amplification of the GBS *cfb* gene, if present, and of the internal control template. The GBS amplicon is a 154-bp DNA fragment. The internal control is a 180-bp DNA fragment consisting of a 134-bp sequence not found in GBS flanked by the complementary sequence of each of the 2 GBS-specific primers. Amplified DNA was detected with hybridization probes labeled with quenched fluorophores (molecular beacons). The fluorophores attached at the 5′ end of the beacons were 5′-carboxyfluorescein and tetrachlorofluorescein for the detection of GBS amplicons and internal control amplicons, respectively. The beacon-target hybrids fluoresce at wave-

lengths characteristic of the fluorophore used in each of the particular molecular beacons used. The concomitant amplification of the internal control allows for verification of the efficiency of the PCR and alerts the user to the presence of significant PCR inhibition within the test sample.

Principle of operation of the SmartCycler automated analyzer. The operation of the SmartCycler is based on the microprocessor-controlled Intelligent Cooling/Heating Optical Reaction (I-Core) module. Each SmartCycler processing block contains 16 independently controlled, programmable I-Core modules, each with 1 reaction site. Up to 6 SmartCycler processing blocks can be daisy-chained together, allowing simultaneous analysis of 96 discrete samples.

Preparation of clinical specimens and controls. The swab sample randomized for the IDI-Strep B test was tested according to manufacturer's instructions. In summary, the swab was placed into a tube containing sample buffer, allowed to stand at room temperature for 5 min, and vortexed at high speed for 15 s. A 50-μL aliquot was then added to the lysis tube and vortexed for 5 min at high speed, followed by centrifugation at low speed for 2–5 s to bring the liquid to the bottom of the tube. The specimen was heated at 95°C for 2 min and placed on ice. From this tube, 1.5 μL (micropipettors and filter-blocked pipettor tips) of the crude cell lysate was transferred to a IDI-Strep B master mix tube, which was previously reconstituted by adding 25 μL of diluent, vortexed for 5 s, and placed at 4°C in the SmartCycler cooling blocks until ready to load on the instrument. The remaining lysate was stored at −20°C for later use as necessary. The loaded reaction tube was centrifuged for 5–10 s in a specially adapted microcentrifuge provided with the SmartCycler before loading. In separate, similar steps, the positive and negative controls of IDI-Strep B were reconstituted with 25 μL of diluent. The controls were also placed at 4°C in the cooling blocks until ready to load on the instrument. Each reaction tube was loaded into an I-Core module of the SmartCycler, and the analysis was conducted according to the SmartCycler operation manual. The unused portion of each lysate was frozen for retesting purposes if necessary.

Definitions and handling of discrepant results. A true-positive IDI-Strep B result was defined as a specimen with a positive result by IDI-Strep B that agreed with culture results. A true-negative IDI-Strep B result was defined as a specimen with a negative result by IDI-Strep B that agreed with culture results. Discrepant results were defined as initial results by IDI-Strep B and culture that did not agree. IDI-Strep B specimens were considered unresolved if there was presence of test inhibitors, as indicated by a failed internal control, an I-Core site failure (optical, thermal, or electronic failure), or invalid assays. The frozen lysates from the unresolved specimens were retested along with positive and negative controls.

Statistical analysis. Results obtained with IDI-Strep B were compared with those obtained by standard broth culture test. The sensitivity and the specificity of IDI-Strep B, as well as 95% CIs, were calculated [25, 26], as were PPVs and NPVs. The χ^2 test was used to compare differences in sensitivity, specificity, NPVs, and PPVs for 3 approaches (IDI-Strep B, antenatal culture, and risk factor approach) compared with intrapartum culture. $P < .05$ was considered significant.

RESULTS

There were 881 women recruited into the study. Of these, 25 either did not receive intrapartum swabbing or have intrapartum swab samples processed, and 53 other women were eliminated because of deviations to the study protocol (22 women had specimens tested by culture >24 h after collection, 26 had reagents of different lots mixed, and 5 had specimens obtained over a whole week that were batched). Thus, 803 enrolled women (91.1% of those recruited) were included in the primary analysis. The median gestational period at delivery was 39 weeks. The overall intrapartum GBS colonization rate across study sites was 18.6% (range, 9.1%–28.7%) based on culture results (table 1). Results of antepartum culture screening were available for 674 of these women (table 2). The median gestational period at specimen collection was 36 weeks. The overall antepartum colonization rate ranged from 8.4% to 15.8%. The performance characteristics of the IDI-Strep B test compared with culture at participating sites are shown in table 3. The sensitivity of IDI-Strep B across study sites ranged from 85% to 99%, specificity ranged from 93% to 100%, PPV ranged from 56% to 100%, and NPV ranged from 94.6% to 99.7%. Inclusion of data from the 53 women with protocol violations in an intention-to-treat analysis led to no significant change in overall results (sensitivity, 93%; [95% CI, 87.7–96.0]; specificity, 96% [95% CI, 94.3–97.2]; PPV, 83.6% [95% CI, 77.4–88.4]; and NPV, 98.4% [95% CI, 97.1–99.1]).

Forty-one discordant results for samples that were negative

Table 1. Rates of intrapartum colonization with group B streptococci among eligable patients at participating study locations.

Site	No. of eligible patients	No. (%) of eligible patients with positive results at the specified site, by intrapartum detection method	
		Culture	IDI-Strep B
Calgary	427	77 (18.0)	88 (20.6)
Houston	75	19 (25.3)	21 (28.0)
Milwaukee	48	13 (27.1)	11 (22.9)
Montreal	166	15 (9.0)	25 (15.1)
Pittsburgh	87	25 (28.7)	22 (25.3)
Overall	803	149 (18.6)	167 (20.8)

NOTE. Overall *P* not significant.

Table 2. Comparison of rates of colonization with group B streptococci at participating study locations.

Site	No. of eligible patients	No. (%) of eligible patients culture-positive for colonization, by timing of detection	
		Intrapartum	Antepartum
Calgary	384	68 (17.7)	45 (11.7)
Houston	57	15 (26.3)	9 (15.8)
Milwaukee	35	8 (22.9)	5 (14.3)
Montreal	143	11 (7.7)	12 (8.4)
Pittsburgh	55	14 (25.5)	8 (14.5)
Overall	674	116 (17.2)	79 (11.7)

NOTE. Only paired specimens were included. Overall $P < .01$.

by culture and positive by IDI-Strep B were obtained. On additional culturing of selective broth, 27 specimens were considered to have truly false-positive IDI-Strep B results on the basis of negative culture results (figure 1). Nine specimens had results that were positive by culture and negative by IDI-Strep B, and these specimens were all considered to have false-negative IDI-Strep B results. Ten specimens were initially unresolved (equivocal). Nine of these specimens were resolved on retesting with IDI-Strep B (8 specimens were negative according to culture and IDI-Strep B, and 1 specimen was positive for GSB according to culture and IDI-Strep B), whereas 1 specimen remained unresolved. Duration of storage of the specimens for up to 24 h was not associated with a change in the rates of discrepant results (data not shown).

Potentially interfering substances (i.e., blood, feces, amniotic fluid, or meconium) were reported for 63% of the collected specimens. In 280 (35%) of the cases, 1 potentially interfering substance was reported; in 206 (26%) of the cases, 2 potentially interfering substances were reported; and in 16 (2%) of the cases, $\geqslant 3$ potentially interfering substances were noted on the collected specimen. Of the 10 initially unresolved specimens, there were no potentially interfering substances in 6 specimens, amniotic fluid in 1, and a combination of potentially interfering substances in 3. For the 1 specimen that could not be resolved, no potentially interfering substances were observed. Presence of potentially interfering substances did not affect the performance characteristics of IDI-Strep B (data not shown).

Antepartum culture screening was performed for 674 women (84%). In another 125 (16%), decisions regarding management of GBS were based solely on use of risk factors without screening (table 4). Compared with intrapartum culture results, IDI-Strep B was superior to both antenatal cultures and prediction of intrapartum status by use of risk factors. For women screened antepartum, the colonization status changed between antepartum screening and intrapartum screening in 69 cases (9%). Of these, colonization status changed from positive to negative in 16 (20%) of 79 and from negative to positive in 53 (9%) of 595. The sensitivity of antepartum cultures in predicting intrapartum culture results ranged from 36% to 63% across the participating centers.

DISCUSSION

The 2002 statement by the CDC on prevention of GBS disease in neonates states that "an adequate rapid intrapartum test must be as sensitive as culture (minimally 85% compared with culture of vaginal and rectal swabs inoculated into selective broth media), rapid, and convenient for integration into routine laboratory use" [10, p. 15]. In this study, we have shown that the molecular IDI-Strep B test is sensitive and specific, compared with culture, and that it meets the criteria set out by the CDC. Furthermore, by using the SmartCycler, which has the ability to process multiple specimens (up to 96) simultaneously, this test may be done in a fashion allowing integration into routine clinical laboratory use.

This study does not provide information on the feasibility of the implementation of rapid testing, because the intrapartum specimens were batched. However, the short duration of the IDI-Strep B test (40-min total) is advantageous for intrapartum

Table 3. Performance characteristics of the IDI-Strep B test for the intrapartum detection of group B streptococci, compared with intrapartum culture, in paired vaginal and anal specimens obtained from 802 pregnant women.

Site	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Calgary	76/77 (99)	338/350 (97)	76/88 (86.4)	338/339 (99.7)
Houston	17/19 (89)	52/56 (93)	17/21 (81.0)	52/54 (96.3)
Milwaukee	11/13 (85)	35/35 (100)	11/11 (100)	35/37 (94.6)
Montreal	14/15 (93)	139/150 (93)	14/25 (56)	139/140 (99.3)
Pittsburgh	22/25 (88)	62/62 (100)	22/22 (100)	62/65 (95.4)
Overall	140/149 (94.0)	626/653 (95.9)	140/167 (83.8)	626/635 (98.6)

NOTE. Data are proportion (%) of specimens with an IDI-Strep B test result confirmed by intrapartum culture. One specimen from the Montreal site gave an initially unresolved result that remained unresolved on retesting and is not included.

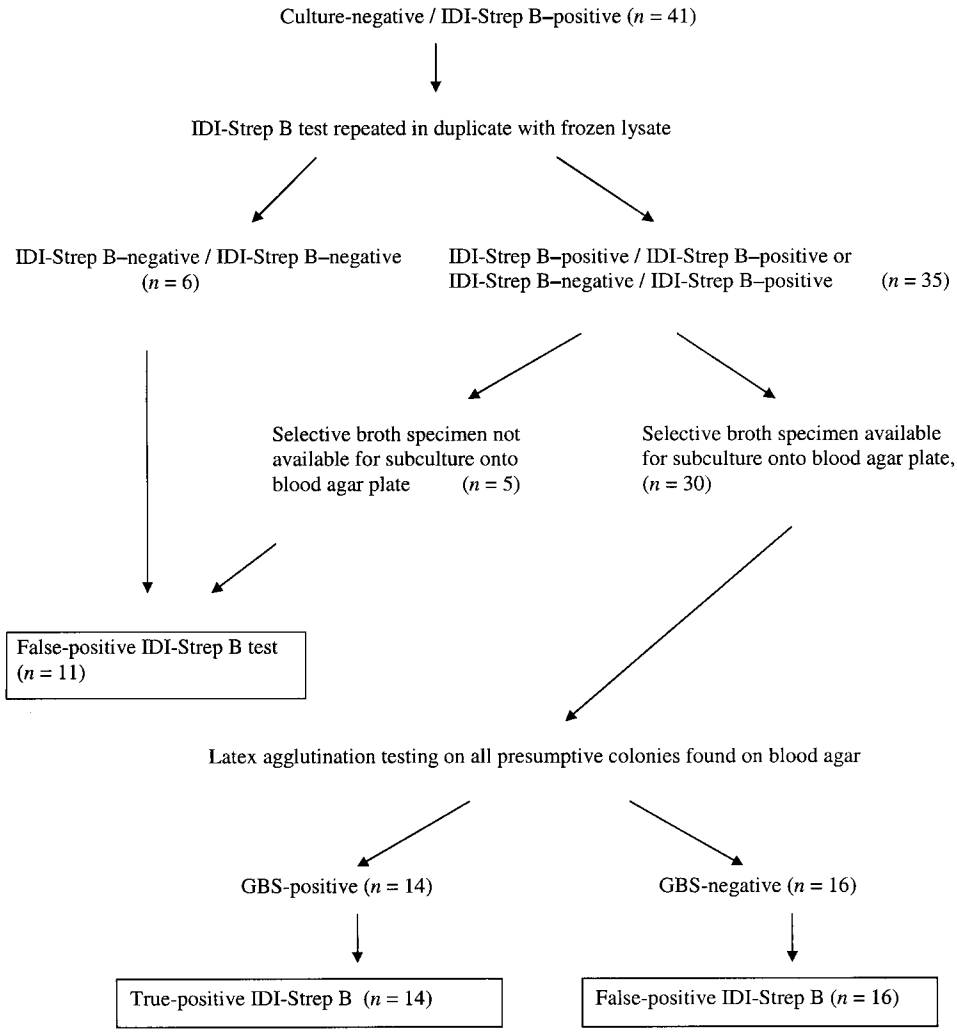

Figure 1. Resolution of discrepant results for 41 swab specimens determined to be negative for group B streptococci (GBS) by culture and positive for GBS by IDI-Strep B.

testing. The setting in which this test is applied and the cost of test [27] would be expected to influence its overall clinical implementation. The test would be useful in the following clinical settings: when there is no opportunity for cultures to be obtained before delivery or culture results are not available at the time of labor; routine antenatal screening in clinical centers in which the specimens can be run immediately to provide an overall short ($\leqslant$2 h) turnaround time; and batch testing of specimens (1 or 2 times a day) from women in preterm labor that is being actively inhibited. An in-house or nearby laboratory with a short transport turnaround time would be needed to meet clinical needs for general routine intrapartum screening to facilitate decision making about administration of antibiotics. For women who deliver before the IDI-Strep B test result is known, the availability of the result may still be useful in identifying whether the delivered infants are at risk of GBS disease.

In our study, ~1% of all specimens were initially unresolved by use of IDI-Strep B, leading to additional testing, which may delay results for this subset of patients. Another potential drawback of the use of the rapid test is that isolates would not be available for susceptibility testing for patients who are allergic to penicillin and who need a different prophylactic antibiotic [10]. For such patients, prenatal screening by culture will need to be continued. Finally, in centers that use the molecular test, periodic surveillance screening of selected women by culture would still be needed to ensure that the GBS isolates remain susceptible to first-line antibiotics.

The IDI-Strep B test performed very well, compared with intrapartum culture, at all participating centers. At the Montreal center, which had the lowest intrapartum culture positivity rate among our centers (9.0%) , a low pretest probability likely resulted in the low PPV of 56% at this center. The variation in GBS colonization rates among pregnant women in different

Table 4. Performance characteristics of the IDI-Strep B test, antepartum culture, and use of risk factors, compared with intrapartum culture, in determining colonization with group B streptococci for 802 pregnant women.

Method	Sensitivity[a]		Specificity[b]		Positive predictive value[b]		Negative predictive value[c]	
	Proportion (%) of specimens[d]	95% CI	Proportion (%) of specimens[d]	95% CI	Proportion (%) of specimens[d]	95% CI	Proportion (%) of specimens[d]	95% CI
IDI-Strep B test	140/149 (94.0)	90.1–97.8	626/653 (95.9)	94.3–97.4	140/167 (83.8)	78.2–89.4	626/635 (98.6)	97.7–99.5
Antepartum culture	63/116 (54.3)	45.3–63.4	542/558 (97.1)	95.7–98.5	63/79 (79.7)	70.9–88.6	542/595 (91.1)	88.8–98.5
Risk factor approach	13/31 (41.9)	24.6–59.3	66/94 (70.2)	61.0–79.5	13/41 (31.7)	17.5–46.0	66/84 (78.6)	69.8–87.3

NOTE. One specimen from the Montreal site had an initially unresolved result that remained unresolved on retesting and is not included.

[a] Overall $P < .0001$ for the difference in proportions between the sensitivity of the 3 approaches. $P < .0001$ for differences in proportions between sensitivities both for IDI-Strep B and antepartum culture and for IDI-Strep B and risk factor approach. No significant difference was seen between antepartum culture and risk factor approach. Results were unchanged if only paired specimens were compared for IDI-Strep B and antenatal cultures.

[b] Overall $P < .0001$ for the difference in proportions between the specificities and between the positive predictive value of the 3 approaches. $P < .0001$ for differences in proportions between specificities and between the positive predictive value both for antepartum culture and risk factor approach and for IDI-Strep B and risk factor approach. No significant difference was seen between IDI-Strep B and antepartum culture for sensitivity or positive predictive value.

[c] Overall $P < .0001$ for the difference in proportions between the negative predictive value of the 3 approaches. $P < .0001$ for differences in proportions between negative predictive value both for IDI-Strep B and antepartum culture and for IDI-Strep B and risk factor approach. $P < .001$ for difference in negative predictive value between antepartum culture and risk factor approach.

[d] Proportion (%) of specimens with a result confirmed by intrapartum culture.

regions is consistent with published literature [6, 12, 28–32]. There were no obvious differences in procedures or in culture methodology that might account for the low prevalence in Montreal. Furthermore, a subset of the specimens from this site with negative results was retested at the central sponsor's laboratory with the same results. This center treats a large percentage of Vietnamese, Chinese, and Middle Eastern women, which may have contributed to the low rates, which are similar to rates previously reported in other Asian populations [33].

The IDI-Strep B test was not affected by the presence of interfering substances, such as blood or meconium, nor did substances associated with rupture of membranes affect it. This confirms the previous report by Bergeron et al. [23]. Just as important, the IDI-Strep B test was superior for predicting intrapartum culture–confirmed GBS colonization status compared with antenatal cultures or use of risk factors. We were particularly surprised with the consistently low sensitivity of antenatal cultures (54%) across all participating centers, compared with the 87% previously reported by Yancey et al. [12]. The reasons for the lower positivity rates in our study are not clear but may reflect the true sensitivity of antepartum cultures in different clinical settings or differences in patient populations or in collection methods. Findings similar to ours have been noted in 2 recent studies [34, 35]. In the first article [34], the sensitivity (calculated from data in the article) of detecting GBS in specimens obtained from pregnant women at 31–36 weeks' gestation was 67% (95% CI, 57–76). The second study [35] did not report sensitivity, but the antepartum PPV was only 67%, compared with 80% in our study and 87% in the study by Yancey et al. [12]. These findings suggest that fewer colonized mothers than previously assumed may be detected in clinical practice at the time of delivery by means of the current approach. This may be partially explained by the timing of some antenatal swabbings, which may occurr earlier than the 35–37 weeks specified by the CDC.

In conclusion, in this prospective multicenter study, we have shown that the IDI-Strep B test was highly sensitive and specific for detecting GBS from combined vaginal and anal specimens obtained from pregnant women in labor. The availability such a test during labor may lead to a further reduction in the rates of neonatal GBS disease.

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