Preventing Early-onset Group B Streptococcal Sepsis: Strategy Development Using Decision Analysis

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ABSTRACT. *Objective.* **To evaluate recommended strategies for prevention of early-onset group B streptococcal infections (EOGBS) with reference to strategies optimized using decision analysis.**

Methods. **The EOGBS attack rate, prevalence and odds ratios for risk factors, and expected effects of prophylaxis were estimated from published data. Population subgroups were defined by gestational age, presence or absence of intrapartum fever or prolonged rupture of membranes, and presence or absence of maternal group B streptococcus (GBS) colonization. The EOGBS prevalence in each subgroup was estimated using decision analysis. The number of EOGBS cases prevented by an intervention was estimated as the product of the expected reduction in attack rate and the number of expected cases in each group selected for treatment. For each strategy, the number of residual EOGBS cases, cost, and numbers of treated patients were calculated based on the composition of the prophylaxis group. Integrated obstetrical-neonatal strategies for EOGBS prevention were developed by targeting the subgroups expected to benefit most from intervention.**

Results. **Reductions in EOGBS rates predicted by this decision analysis were smaller than those previously estimated for the strategies proposed by the American Academy of Pediatrics in 1992 (32.9% vs 90.7%), the American College of Obstetricians and Gynecologists in 1992 (53.8% vs 88.8%), and the Centers for Disease Control and Prevention in 1996 (75.1% vs 86.0%). Strategies based on screening for GBS colonization with rectovaginal cultures at 36 weeks or on use of a rapid test to screen for GBS colonization on presentation for delivery, combining intrapartum prophylaxis for selected mothers and postpartum prophylaxis for some of their infants, would require treatment of fewer patients and prevent more cases (78.4% or 80.1%, respectively) at lower cost.**

Conclusions. **No strategy can prevent all EOGBS cases, but the attack rate can be reduced at a cost <$12 000 per prevented case. Supplementing intrapartum prophylaxis with postpartum ampicillin in a few infants is more effective and less costly than providing intrapartum prophylaxis for more mothers. Better intrapartum screening tests offer the greatest promise for increasing efficacy. Integrated obstetrical and neonatal regimens appropriate to the population served should be adopted by each obstetrical service. Surveillance of costs, complications, and benefits will be essential to guide continued iterative improvement of these strategies.** *Pediatrics* **1999;103(6). URL: http://www.pediatrics.org/cgi/content/full/103/6/e76;** ***group B streptococcus, neonatal sepsis, early-onset sepsis, prevention, decision analysis.***

ABBREVIATIONS. CDC, Centers for Disease Control and Prevention; EOGBS, early-onset neonatal GBS infection; ACOG, American College of Obstetricians and Gynecologists; AAP, American Academy of Pediatrics; GBS, group B streptococcus; PROM, prolonged rupture of membranes (>18 hours).

Publication of recommendations for "Prevention of Perinatal Group B Streptococcal Disease" by the Centers for Disease Control and Prevention (CDC)[1] created an imperative for adoption of strategies for prevention of early-onset neonatal group B streptococcal (EOGBS) infections by every institution at which infants are delivered. This consensus statement has been endorsed by the Committee on Obstetric Practice of the American College of Obstetricians and Gynecologists (ACOG)[2] and by the Committees on Infectious Diseases and on the Fetus and Newborn of the American Academy of Pediatrics (AAP).[3] Two strategies for treatment of pregnant women are recommended: one based on late prenatal screening cultures and one based on clinical risk factors. Intrapartum antibiotic prophylaxis using these strategies was estimated to reduce the attack rates for EOGBS by 86.0% and 68.8%, respectively,[4] establishing a de facto national target of reduction of the incidence of this disease. The ACOG endorsement[2] includes an admonition that "lack of prompt availability of culture results may render use of late prenatal cultures impractical" and notes that "if the results of prenatal cultures are not available, intrapartum prophylaxis should be offered only based on the presence of intrapartum risk factors for early-onset group B streptococcus disease," suggesting a continued preference for the "risk factor-based" strategy originally advocated by ACOG in 1992.[5] The CDC recommendations also provide an example of a protocol for treatment of infants whose mothers have received intrapartum antibiotic prophylaxis.[1] The AAP endorsement suggests a similar but not identical regimen for these infants.[3] Both state that "variations that incorporate individual circumstances or institutional preferences may be appropriate," so these recommendations cannot be implemented without further elaboration. The consensus sought by the CDC, the ACOG, and the AAP remains elusive, as Gotoff and Boyer[6] have recently proposed a

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different strategy for group B streptococcus (GBS) prevention, and Siegel and Cushion[7] and Wedgwood et al[8] have recently advocated universal postpartum prophylaxis.

Seeking to understand the basis for recommended strategies for GBS prevention, we examined previously published comparisons of alternative strategies. There have been no clinical trials of any of the proposed strategies,[2] but several cost-benefit studies[9–13] and decision models[4] are available. Most are flawed by an explicit[10,12] or implicit[9,11,13] assumption that intrapartum antibiotic prophylaxis prevents all cases of EOGBS, which is inconsistent with reports of proven neonatal GBS sepsis after intrapartum antibiotic administration.[14–17] The most comprehensive analysis, which provided much of the basis for the CDC recommendations, more conservatively assumed an attack rate of 1 per 1000 live births after intrapartum prophylaxis of women with GBS colonization, but did not stratify risk according to gestational age.[4] We therefore undertook this analysis of the benefits and costs of strategies for prevention of neonatal GBS disease. Estimation of the population-wide cost and effectiveness of any prevention strategy requires knowledge of the overall EOGBS attack rate, the prevalence of and risk associated with clinical factors used for selection of parturients or neonates for prophylaxis, the effects of interventions that may be used, and the costs of screening tests and antimicrobial prophylaxis regimens included in the prevention strategy. Estimates for these parameters, determined by critical analysis of published data[18,19] or obtained from our hospital cost-accounting system, were used in a decision analysis to estimate treatment requirements, GBS attack rates, and implementation costs for strategies for prevention of EOGBS disease. This analysis was used to evaluate, refine, and develop alternatives to previously advocated GBS prevention strategies.

METHODS

Model Parameters

All models are based on vaginal and rectovaginal colonization rates of 14.7% and 22.8%,[20] respectively, and an overall attack rate of 3 cases per 1000 live births.[18] Clinical variables associated with increased risk of EOGBS[18] and effects of interventions[19] were identified and evaluated by comprehensive literature review. Only statistically significant, independent factors routinely available in clinical practice were considered, reducing the variables used for risk stratification to estimated gestational age, intrapartum factors (rupture of membranes >18 hours or intrapartum maternal fever), and maternal GBS colonization. GBS colonization could be ascertained at 26 to 28 or at 35 to 37 weeks gestation by antepartum rectovaginal culture or on presentation for delivery by vaginal culture or a rapid screening test (Strep B OIA; Biostar, Boulder, CO). Table 1 shows the prevalence of and odds ratios associated with each of these factors. Intrapartum prophylaxis alone[21–25] or in combination with postpartum prophylaxis[26,27] were estimated to reduce the EOGBS attack rate by 80.2% or by 95.0%, respectively, and postpartum prophylaxis alone[7] was expected to reduce it by 68.8%.[19]

Estimates for direct costs (Table 2) were obtained from the hospital management information system (Transition Systems, Inc, Boston, MA) at Lucile Packard Children's Hospital. Costs of maternal prophylaxis were based on costs to the hospital of $1.80 and $2.80 for 1 and 2 g vials of ampicillin, respectively, $2.25 for incidental supplies (syringe, diluent, alcohol swabs, and so forth), an average cost for initiation and maintenance of an intravenous fluid infusion of $40, an average of three doses per patient, and assumption that 40% of parturients do not have intravenous access for other purposes. Costs for treatment of maternal complications were calculated from the probabilities and costs of minor allergic reactions, anaphylaxis, and maternal death used by Rouse et al,[4] and incorporated into the average cost estimate in Table 2. The cost of neonatal antibiotic prophylaxis was based on costs of $1.00 per 125 or 250 mg vial of ampicillin and $2.25 for incidental supplies; estimates assumed a single dose for infants given postpartum prophylaxis alone[6] or four doses before hospital discharge for those given both intrapartum and postpartum prophylaxis.[26,28] Estimated costs of screening tests, including both materials and laboratory personnel, were based on actual costs of performing these tests at Lucile Packard Children's Hospital. No other incremental personnel costs were included, because it was assumed that prophylaxis for mothers and infants can be provided without increased staffing of the labor and delivery suite, normal newborn nursery, or hospital pharmacy. No attempt was made to estimate the costs of not providing prophylaxis (see "Discussion"). Cost estimates do not include potential costs of prolonging the hospital stay to permit extended observation or treatment of infants at risk.

TABLE 1. Risk Factors Associated With Early-onset Neonatal Group B Streptococcal Infection

Risk Factor	Prevalence (%)	Odds Ratio
Estimated gestational age		
<28 weeks	0.8	21.7
28–30 weeks	0.9	10.0
31–33 weeks	2.1	4.65
34–36 weeks	6.5	2.19
≥37 weeks	89.7	1.00
Intrapartum fever or PROM	6.8	11.5
Maternal GBS colonization:		
+ Rectovaginal culture at 35–37 weeks*	20.4	26.7
+ Vaginal culture at delivery	14.7	204
+ Strep B OIA at delivery	16.6	15.4

Abbreviations: PROM, prolonged rupture of membranes; GBS, group B streptococcus.
* Prevalence reflects a rectovaginal colonization rate of 22.8% in the 89.7% of parturients who deliver at term; odds ratio applies only to screened infants.

TABLE 2. Estimated Costs of Prophylaxis for Neonatal Group B Streptococcal Sepsis

Intervention	Cost
Screening rectovaginal cultures for GBS	$20
Strep B OIA rapid test	$13
Maternal intrapartum antibiotics	$29
Neonatal antibiotic prophylaxis	$13

Abbreviation: GBS, group B streptococcus.

Model Development

Decision analysis[29] was used to assess the effects of prevention strategies on the prevalence of EOGBS in an entire population. The decision analysis was based on subdivision of the population into ≤20 risk groups characterized by five gestational age ranges (<28, 28–30, 31–33, 34–36, and ≥37 weeks), presence or absence of maternal GBS colonization, and the presence or absence of intrapartum factors (fever or prolonged rupture of the membranes [PROM]). The probability of each possible combination of risk factors is the product of the probabilities (or prevalences) of the individual risk factors. For example, if probability of intrapartum risk factors is 6.8%, the probability of a positive Strep B OIA screening test (Biostar, Boulder, CO) is 16.6%, and the probability of delivering at term is 89.7%, the probability of having all three of these findings is 0.0101 ($0.068 \times 0.166 \times 0.897$). Bayesian principles were applied to distribute expected EOGBS cases for the population among the subgroups defined by combinations of risk factors as above, in accordance with the postulated prevalence and odds ratio for each risk factor.[30] The number of EOGBS cases predicted to be prevented by an intervention was determined by

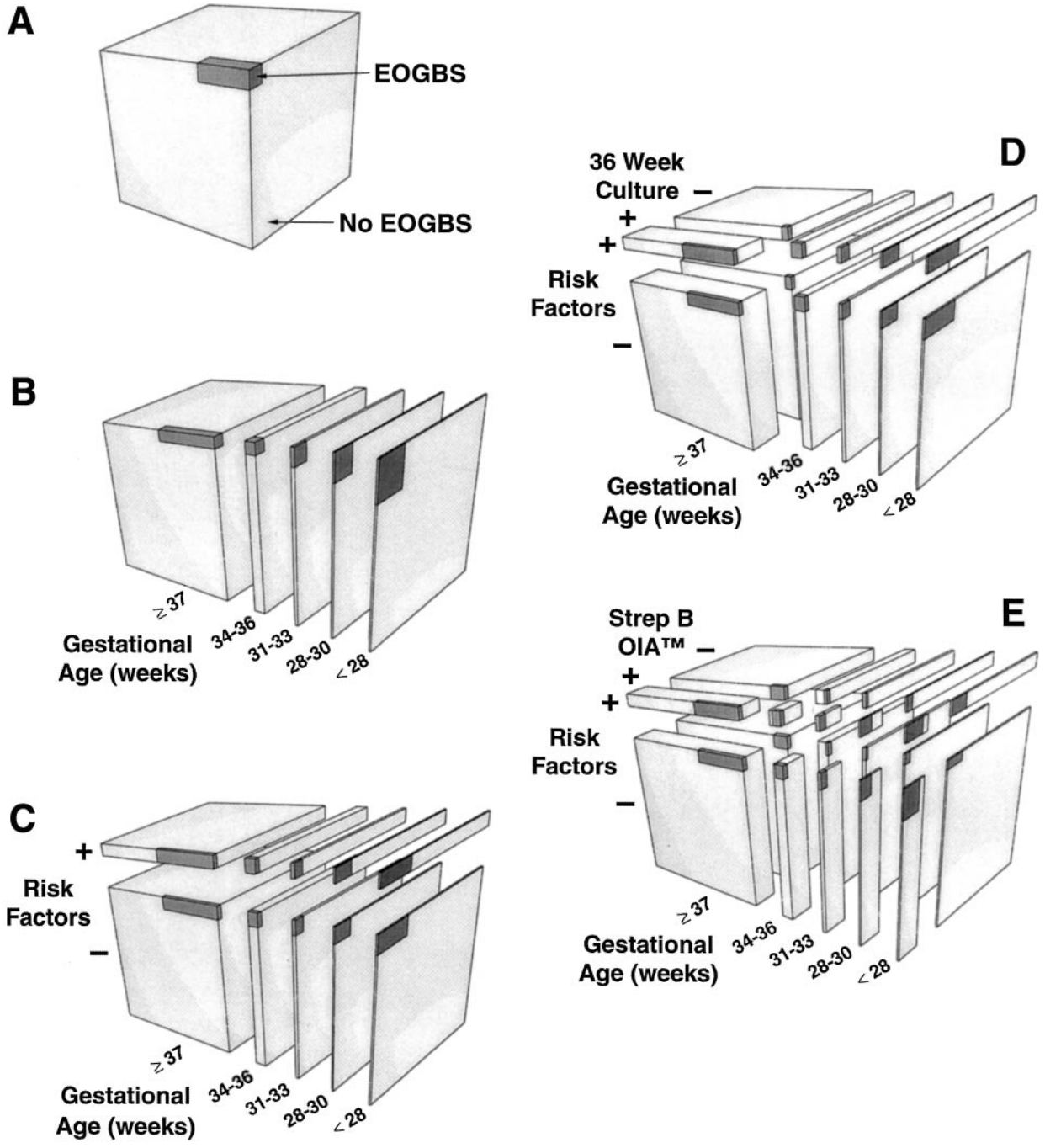

Fig 1. Allocation of risk for neonatal group B streptococcal sepsis. A: Representation of an attack rate for early-onset group B streptococcal (EOGBS) sepsis of 3 cases per 1000 live births. Infants with infection represented by darker shading (block $1 \times 1 \times 3$ units) in a population represented by a $10 \times 10 \times 10$ unit block (lighter shading). B: Distribution of the risk of EOGBS disease among groups defined by gestational age; proportionately larger regions with dark shading denote increasing risk with decreasing gestational age. C: Allocation of the risk of EOGBS disease shown in B among groups defined by the presence (+) or absence (−) of intrapartum risk factors (intrapartum fever or rupture of membranes >18 hours). D and E: Allocation of the risk of EOGBS disease shown in C among groups defined by the presence (+) or absence (−) of maternal colonization, as ascertained by antepartum rectovaginal culture at ~36 weeks (D) or by testing of vaginal swabs obtained on presentation for delivery using the Strep B OIA (Biostar, Boulder, CO) rapid screening test (E).

multiplying the expected fractional reduction in attack rate by the number of EOGBS cases expected in the subgroup selected for treatment. For each strategy, the number of residual EOGBS cases, cost, and numbers of treated patients were calculated by summation of these quantities for all patient subgroups.

Sensitivity Analysis

The effects of changes in clinical parameters on the implications of this decision analysis were assessed by varying values used for the population attack rate, effectiveness of interventions, and cost estimates across the range of possible values.[29] Effects of screening test performance were assessed using a model based on an idealized rapid screening test with sensitivity and specificity equivalent to those of intrapartum vaginal cultures.

RESULTS

The proportion of the population included and the expected attack rates for each of 20 risk groups defined by gestational age, intrapartum risk factors,

TABLE 3. Proposed Strategies for Prevention of Early-onset Neonatal Group B Streptococcal Infections

Prevention Strategy	AAP, 1992[31]	ACOG, 1992 and CDC-AAP-ACOG, 1996 (Option 2)[1]	CDC-AAP-ACOG, 1996 (Option 1)[1]	Gotoff and Boyer[6]	Universal Intrapartum Prophylaxis
Screening for GBS colonization	Rectovaginal culture at 28 weeks	None	Rectovaginal culture at 35–37 weeks	Rectovaginal culture at 35–37 weeks	None
Criteria for intrapartum prophylaxis	GBS screen + *and* EGA <37 weeks or risk factor* +	EGA <37 weeks *or* risk factor* +	GBS screen + *or* EGA <37 weeks *or* risk factor* + and GBS status unknown	GBS screen + *and* risk factor* or delivery before GBS screening done	All parturients
Criteria for neonatal prophylaxis	—	—	—	GBS screen +	—
Patients treated per 1000 births	37	171	307	323†	1000
Patients treated per case prevented	38	106	136	142	415
GBS cases prevented (%)	32.9	53.8	75.1	75.6	80.2
Cost per case prevented	$22 215	$3067	$11 925	$9720	$12 049

Abbreviations: AAP, American Academy of Pediatrics; ACOG, American College of Obstetricians and Gynecologists; CDC, Centers for Disease Control and Prevention; GBS, group B streptococcus; +, positive.
* Prolonged rupture of membranes >18 hours or intrapartum maternal fever >38°C.
† 118.4 mothers and 204.3 infants.

and screening tests for maternal vaginal colonization are shown in Fig 1. The block in Fig 1A represents 3 EOGBS cases (dark shading) in a total of 1000 infants. In Fig 1B, these cases are allocated among subgroups according to gestational age; for example, 12.0% of EOGBS cases occur in the 0.8% of the population with gestational ages <28 weeks (attack rate 44.8 per 1000) and 64.5% occur in the 89.7% of the population ≥37 weeks gestation (attack rate 2.16 per 1000). The probabilities of EOGBS and the proportions of the population included in each risk group shown in Fig 1 are detailed in the Appendix. The risk distribution based on use of rectovaginal cultures at 26 to 28 weeks gestation[31] was also calculated (not shown).

Table 3 summarizes the number of cases prevented, number of parturients treated, and associated costs for the strategies proposed by the AAP in 1992,[31] the ACOG in 1992,[5] the CDC in 1996,[1] and Gotoff and Boyer in 1997,[6] or for universal prophylaxis. Universal intrapartum prophylaxis would prevent only 80.2% of expected cases, reflecting the incomplete efficacy of this intervention, at a cost of $12 049 per case prevented. The now obsolete strategy recommended by the AAP[31] in 1992 is the most expensive, at a cost of $22 215 per case prevented, and the least effective of these regimens, preventing only approximately one-third (32.9%) of the expected cases. The risk factor strategy originally recommended by ACOG[5] and included as option 2 in the CDC recommendations[1] is much less costly ($3067 per case prevented) and more effective, but prevents only slightly more than half (53.8%) of the expected GBS cases. CDC option 1, which is based on antepartum screening cultures at 35 to 37 weeks,[1] prevents nearly as many cases as universal intrapartum prophylaxis (75.1%) and is slightly less expensive ($11 925 per case prevented), but requires treatment of more than 30% of all parturients. The combined approach of Gotoff and Boyer,[6] in which ~10% of parturients and 20% of infants receive prophylaxis, is equally effective (75.6%) and less expensive ($9720 per case prevented).

For each of the risk groups shown in Fig 1, the proportion for which EOGBS would be prevented by intrapartum antibiotic prophylaxis alone or by addition of postpartum prophylaxis were calculated (Fig 2). As shown in Fig 2A, the analysis predicts that intrapartum prophylaxis would prevent the majority of the EOGBS cases expected to occur in nearly one-fourth of the infants born to mothers with intrapartum fever or PROM before 28 weeks gestation, but would be of little benefit for infants born to mothers without intrapartum risk factors after 34 weeks gestation, who are unlikely to become infected. Screening for maternal GBS colonization increases the range of predicted benefits (Fig 2B and 2C). For example, screening of infants delivered before 28 weeks gestation for GBS colonization by Strep B OIA at the time of delivery allows recognition of a very high risk group (whose mothers are both GBS colonized and have an intrapartum risk factor) in which intrapartum prophylaxis will prevent EOGBS in more than half of all infants (Fig 2C). In contrast, very few term infants whose mothers have neither GBS-colonization (whether identified by rectovaginal culture at 35 to 37 weeks or by OIA) nor intrapartum risk factors will benefit from prophylaxis (Fig 2B and 2C, respectively).

With this information, efficient prevention protocols can be developed by designating risk groups for prophylaxis in order of decreasing benefit. The characteristics of these groups depend on the method used to screen for GBS colonization. Construction of prevention protocols based on gestational age and intrapartum risk factors is demonstrated in Fig 3 and Table 4. Figure 3 shows the relationship between the percentage of EOGBS cases prevented (a benefit of intervention) and the number of women given intrapartum prophylaxis (a measure of cost) for all possible strategies based on these risk indicators. In the

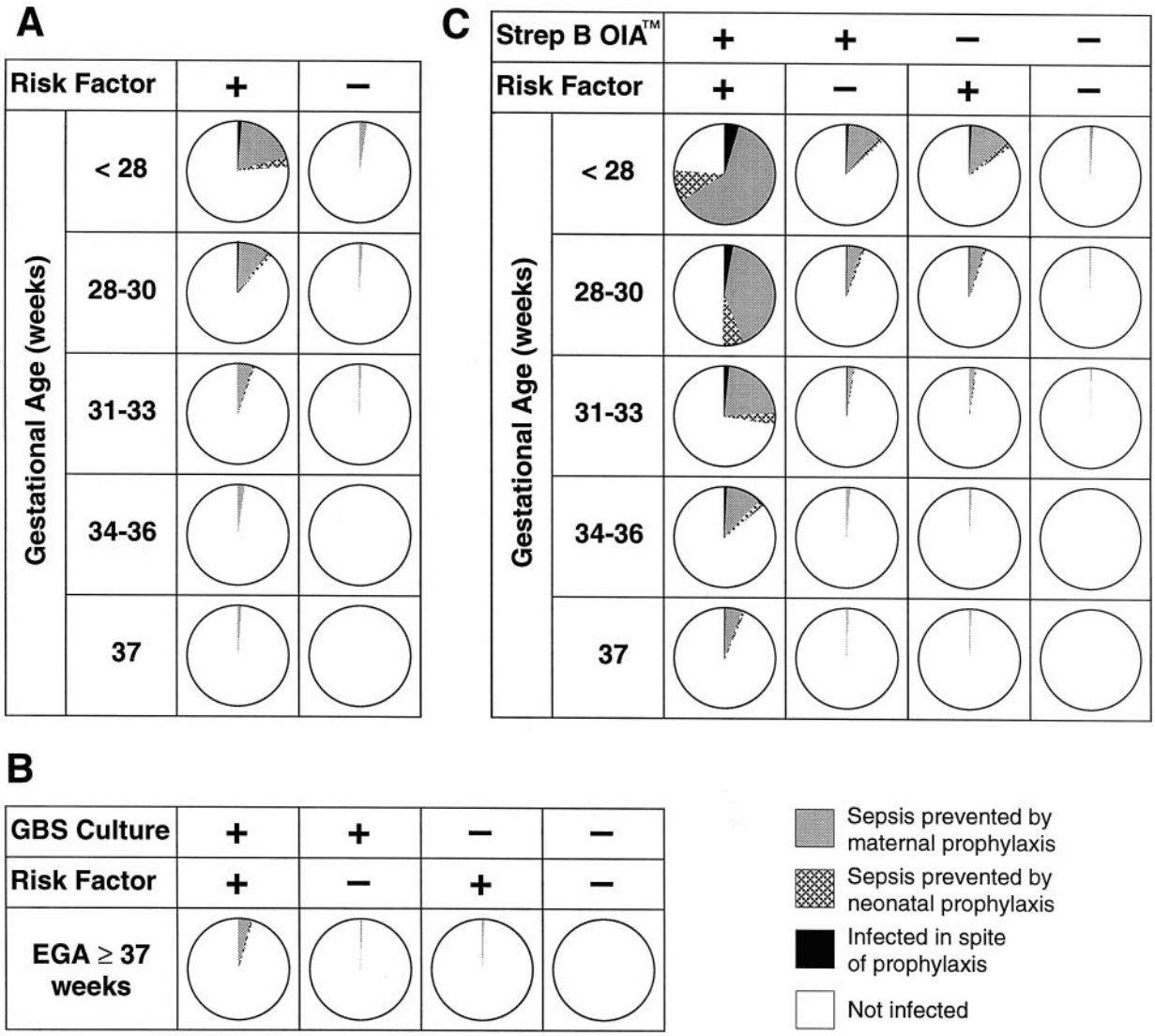

Fig 2. Allocation of benefits from intrapartum or combined intrapartum and postpartum prophylaxis. Risk groups were defined by gestational age, the presence (+) or absence (−) of intrapartum risk factors (intrapartum fever or rupture of membranes >18 hours), and the presence (+) or absence (−) of maternal colonization, as ascertained by rectovaginal culture at ~36 weeks (B) or by testing of vaginal swabs obtained on presentation for delivery using the Strep B OIA (Biostar, Boulder, CO) rapid screening test (C). The proportion of infants in each group expected to be uninfected even without prophylaxis (white), have infection prevented by intrapartum prophylaxis (gray) or by addition of postpartum prophylaxis (cross-hatch), or have infection despite both intrapartum and postpartum prophylaxis (black) is indicated.

first possible strategy, only women delivering before 28 weeks gestation with intrapartum risk factors are designated for intrapartum prophylaxis (Fig 3, lower left). For the second and third potential strategies, women at successively more advanced gestations (28–30 and 31–33 weeks, respectively) are also selected for intrapartum prophylaxis. The fourth strategy, however, designates infants <28 weeks gestation whose mothers have intrapartum risk factors for postpartum prophylaxis, because that intervention will prevent EOGBS in a larger proportion of those infants than can be expected with intrapartum prophylaxis for any remaining group of mothers. For each strategy developed by this sequential inclusion of groups yielding the greatest incremental benefit, the rules used to recognize groups designated for prophylaxis follow from, rather than dictate, the characteristics of the patient groups selected for prophylaxis.

For each of the 84 possible prevention strategies based on risk factors alone, based on screening for GBS colonization with antepartum rectovaginal cultures, or based on intrapartum screening using the Strep B OIA, the number of women and infants treated (per 1000 live births and per case prevented) and the anticipated total and marginal costs per case prevented were calculated. The marginal cost represents the cost of preventing one EOGBS case in the lowest risk group treated in each strategy. These costs are plotted against the expected reduction of the EOGBS rate (ie, benefit) in Fig 4. To prevent any specific fraction of the expected EOGBS cases, fewer women are treated in strategies based on screening for GBS colonization than in risk-only strategies, and the fewest are treated in strategies based on intrapartum screening (Fig 4A). The relationship between choice of screening method and the number of infants who must be treated to prevent a given pro-

portion of EOGBS cases is similar (Fig 4B) but less consistent, because the number of infants treated depends on the number of mothers who are treated to achieve the observed result. Reductions in the number of treated mothers or infants per case prevented with increasing efficacy are a consequence of additional benefits accruing from treatment of more individuals in the other category (Fig 4C and 4D). The risk factor strategy is less expensive than screening-based strategies for reductions in attack rate <65%, but is of comparable or greater cost for more effective strategies (Fig 4E). Strategies using the Strep B OIA cost less than those using antepartum cultures (Fig 4E). Reductions in cost despite increasing efficacy (Fig 4F) result from elimination of screening tests as more groups are designated for treatment; if all infants in a gestational age category are to be treated, independent of GBS colonization status, for example, screening for colonization becomes unnecessary.

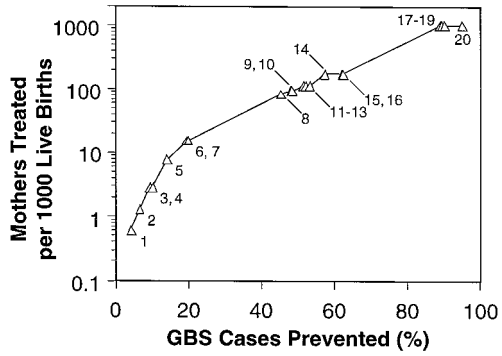

Fig 3. Construction of strategies for prevention of early-onset group B streptococcus based on gestational age and intrapartum risk factors. Percentage of early-onset group B streptococcus cases prevented is plotted against number of women given intrapartum antimicrobial prophylaxis for each potential prevention strategy. From the lower left to upper right, each symbol (△) represents addition of the patient subgroup with the greatest predicted benefit to those already designated for prophylaxis. Strategies are numbered sequentially, corresponding to the characteristics of the last patient group added and the prophylaxis measure applied in each successive strategy as shown in Table 4.

The optimal strategies selected from these numerous candidates may depend on the desired benefit, maximum marginal costs, or other criteria. Both the number of infants requiring treatment (Fig 4D) and marginal cost per case prevented (Fig 4F) increase rapidly as reductions in GBS disease rates exceed 80%, in which the cost per case prevented for strategies based on screening for maternal colonization is at a minimum (Fig 4E). For strategies based on intrapartum screening using the Strep B OIA, an 80% reduction in attack rate requires prophylaxis for all risk groups in which the intervention will prevent EOGBS in at least 0.25% of the infants. To compare strategies with equivalent marginal costs, the criterion of treating all risk groups in which intervention prevents EOGBS in at least 0.25% of the infants was used to select strategies based on risk factors alone, based on screening for GBS colonization with antepartum rectovaginal cultures, or based on an idealized intrapartum test with performance characteristics equivalent to intrapartum vaginal cultures. The characteristics of the patients selected for prophylaxis, which translate directly to rules for their clinical identification, and the predicted effects of strategies selected using this criterion are shown in Table 5.

Parameter Estimates

The results of this analysis depend on the postulated attack rates, prevalences and odds ratios for risk factors, and effectiveness of interventions. To determine if the selection of different values for parameters for any of these four categories would change our conclusions, we assessed the effects of substituting values at the extremes of their plausible ranges. We found that the results shown in Tables 4 and 5 can be extrapolated to

TABLE 4. Construction of Strategies for Prevention of EOGBS Based on Gestational Age and Intrapartum Risk Factors

Strategy	Last Subgroup Designated for Prophylaxis				Cumulative Effects of Strategy		
	Gestational Age (Weeks)	Intrapartum Risk Factors	Intervention	% in Which EOGBS Is Prevented	Mothers Treated per 1000 Births	Infants Treated per 1000 Births	EOGBS Cases Prevented (% of Expected)
1	<28	+	Intrapartum	20.337	0.60	0.00	4.1
2	28–30	+	Intrapartum	10.385	1.28	0.00	6.5
3	31–33	+	Intrapartum	5.053	2.87	0.00	9.1
4	<28	+	Postpartum	3.727	2.87	0.60	9.9
5	34–36	+	Intrapartum	2.436	7.78	0.60	13.9
6	<28	−	Intrapartum	2.226	15.18	0.60	19.4
7	28–30	+	Postpartum	1.903	15.18	1.28	19.8
8	≥37	+	Intrapartum	1.122	82.95	1.28	45.1
9	28–30	−	Intrapartum	0.990	91.27	1.28	47.9
10	31–33	+	Postpartum	0.926	91.27	2.87	48.4
11	31–33	−	Intrapartum	0.451	110.68	2.87	51.3
12	34–36	+	Postpartum	0.447	110.68	7.78	52.0
13	<28	−	Postpartum	0.408	110.68	15.18	53.0
14	34–36	−	Intrapartum	0.221	170.77	15.18	57.2
15	≥37	+	Postpartum	0.206	170.77	82.95	61.9
16	28–30	−	Postpartum	0.182	170.77	91.27	62.4
17	≥37	−	Intrapartum	0.096	1000.00	91.27	88.8
18	31–33	−	Postpartum	0.082	1000.00	110.68	89.3
19	34–36	−	Postpartum	0.039	1000.00	170.77	90.1
20	≥37	−	Postpartum	0.018	1000.00	1000.00	94.9

Abbreviation: EOGBS, early-onset neonatal group B streptococcus infection.

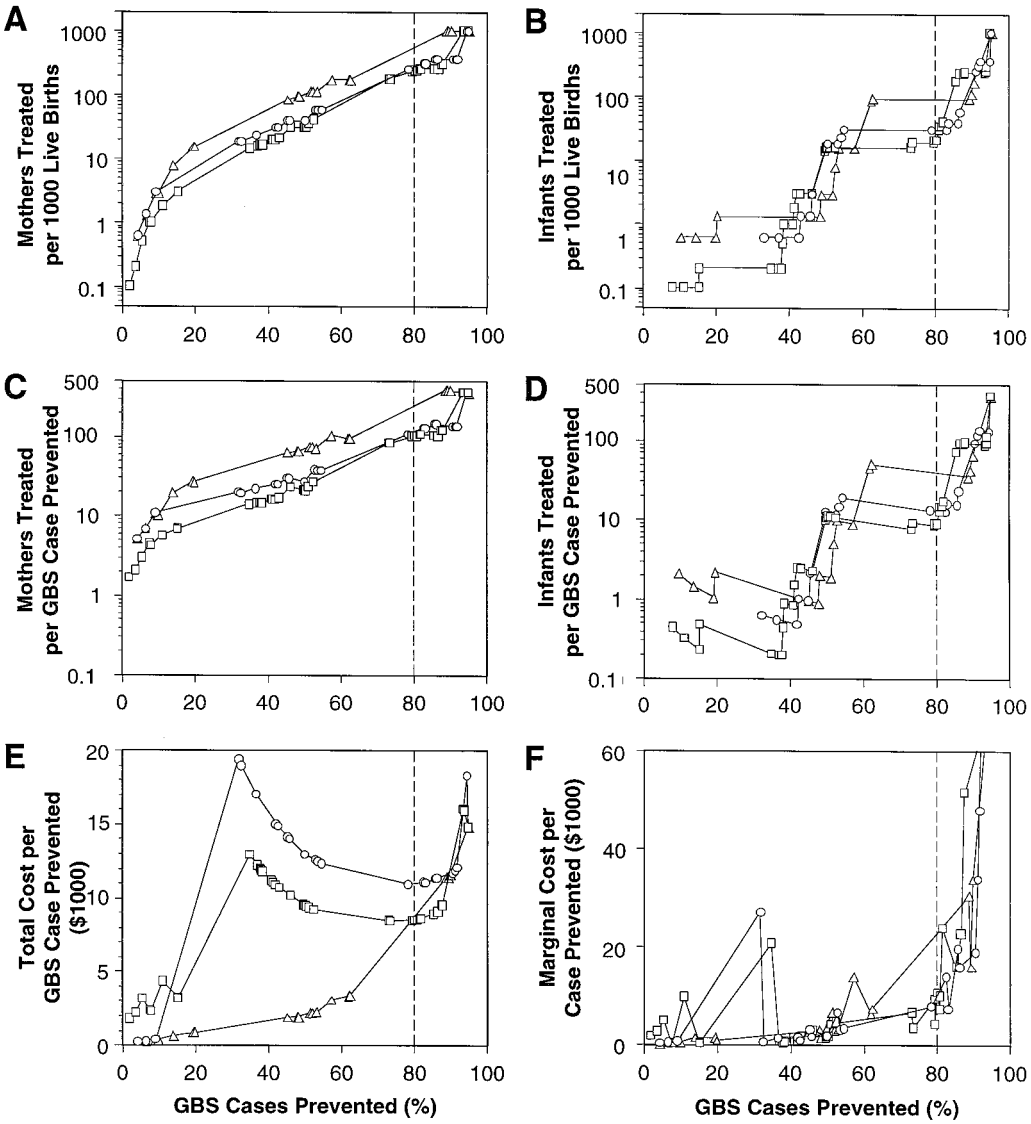

Fig 4. Costs and benefits of strategies for prevention of early-onset group B streptococcal disease based on alternative methods for ascertainment of maternal group B streptococcus (GBS) colonization. Strategies based on risk factors alone (△), screening for GBS colonization using rectovaginal culture at 35 to 37 weeks' gestation (○), or screening for GBS colonization using the Strep B OIA (Biostar, Boulder, CO) rapid screening test on presentation for delivery (□) were constructed by sequential selection of risk groups (defined by gestational age, intrapartum risk factors, and maternal GBS colonization) for either intrapartum or combined prophylaxis as described in the text. Broken vertical lines indicate the objective of an 80% reduction in early-onset group B streptococcus cases.

populations with different EOGBS attack rates, because changing the presumed population attack rate had almost no effect on risk distribution, total cost, or the proportion by which the attack rate is reduced, but would proportionately change the absolute number of cases prevented by any strategy. Reducing the projected attack rate from 3 to 1 per 1000 live births, for example, does not affect the expected proportionate reduction in EOGBS cases, but triples the cost of preventing one case.

Changes in the proportions by which prophylactic measures are expected to reduce the rate of EOGBS disease lead to corresponding changes in the number of cases prevented by each intervention. If the effectiveness of intrapartum or combined intrapartum and postpartum prophylaxis are changed independently, their relative benefits and the risk groups selected for prophylaxis may change substantially. For example, there would be no rationale for use of combined prophylaxis in the highest risk groups if addition of postpartum prophylaxis produces little increase in efficacy greater than that of intrapartum prophylaxis alone, but it might be appropriate or necessary to provide postpartum ampicillin prophylaxis to a larger number of neonates if the difference in efficacy between these approaches is greater than the 15% used in this model.

Changes in the costs of screening or treatment have no effect on the clinical benefits of different screening or prophylaxis strategies. The lower cost of strategies based on the Strep B OIA compared with those using rectovaginal cultures is mostly related to the lower estimated cost of the rapid screening test. If these tests have the same costs, strategies based on the Strep B OIA are still less expensive (eg, $8443 vs $8743 per prevented case for the strategies of Table 5 if both cost

TABLE 5. Integrated Strategies for Prevention of Early-Onset Neonatal Group B Streptococcal Infections

Screening for GBS Colonization	None	Rectovaginal Culture at 35–37 Weeks	Strep B OIA at Delivery	Ideal Intrapartum Screening Test
Criteria for intrapartum prophylaxis	EGA <34 weeks *or* Risk factor* +	EGA <34 weeks *or* GBS culture + *or* EGA <37 weeks and risk factor* +	EGA <31 weeks *or* Strep B OIA + *or* Risk factor* +	GBS screen + *or* EGA <31 weeks and risk factor* +
Criteria for neonatal prophylaxis	EGA <28 weeks *or* EGA <37 weeks and risk factor* +	EGA <28 weeks *or* Two of: EGA <37 weeks Risk factor* + GBS culture +	Two of: EGA <34 weeks Strep B OIA + Risk factor* +	GBS screen + and risk factor* + *or* GBS screen + and <37 weeks *or* Risk factor* + and <28 weeks
Women treated per 1000 births	111	247	242	148
Neonates treated per 1000 births	15	31	21	26
Women treated per case prevented	70	105	101	55
Neonates treated per case prevented	10	13	9	10
GBS cases prevented (%)	53.0	78.4	80.1	89.6
Cost per case prevented	$2142	$10 843	$8443	$9168

Abbreviation: GBS, group B streptococcus.
* Prolonged rupture of membranes >18 hours or intrapartum fever >38.0°C.

$13). Rapid screening strategies become more expensive than culture-based approaches only if the cost of the Strep B OIA exceeds that of a culture by more than ~5%. Changes in the costs of antibiotic therapy affect overall costs of integrated (mother and infant) intervention strategies nearly uniformly, but are relatively modest, because the majority of costs are attributable to screening for GBS colonization. Doubling the cost of ampicillin would increase the cost from $10 843 to $11 577 per case prevented for the antepartum screening strategy (Table 5), or from $8443 to $9117 per case prevented for the antepartum screening strategy.

DISCUSSION

Controversy surrounding obstetrical treatment of women at risk for transmitting GBS colonization to their newborn infants escalated after publication of an educational advisory statement by the ACOG[32] and Guidelines for Prevention of Group B Streptococcal Infection by the American Academy of Pediatrics[31] in 1992. These recommendations were at odds, with ACOG advising against antenatal screening and the AAP advocating screening for GBS colonization using maternal rectovaginal cultures at 26 to 28 weeks gestation. The AAP recommended prophylaxis for the few (<4%) parturients who have both GBS colonization and clinical risk factors, but ACOG supported intrapartum treatment of all parturients with clinical risk factors (≈15% of women). Despite commentaries and clarifications, these differences were not resolved. While the medical community was occupied with this debate, the Group B Strep Association, whose membership includes many parents who have lost infants to neonatal GBS infections, applied intense political pressure seeking issuance of national guidelines. Draft guidelines were published in the Federal Register in December of 1994, eliciting a flood of more than 4000 letters to the CDC.[1,33] A consensus conference organized by the CDC and the California Department of Health Services in March of 1995 reviewed and refined this draft, ultimately resulting in issuance of CDC recommendations in May of 1996.[1] The CDC statement deems two different maternal prophylaxis strategies to be appropriate "until further data become available to define the most effective strategy," and provides an example of one approach to treatment of infants whose mothers have received intrapartum prophylaxis, along with the statement that "evaluation of alternative approaches remains appropriate".[1] However, it is unlikely that new data will soon be available, because the number of patients needed for a randomized controlled trial of GBS prevention has been estimated to be as many as 2.5 million patients per treatment group.[34] Optimal use of existing data to guide practice recommendations is therefore imperative. We undertook comprehensive literature reviews to establish the identity, prevalence, and magnitude of risk factors associated with EOGBS,[18] and to quantitate potential benefits of preventive interventions.[19] These estimates were used for this decision analysis.

This decision analysis attempts to address the shortcomings of previous models, which include overestimation of the effectiveness of antibiotic prophylaxis,[4,9–13] inconsistency between implicit estimates of the GBS colonization rates at screening and delivery,[11,12] failure to stratify risk by gestational age,[4,11] overlooking the significance of differences between vaginal and rectovaginal colonization rates,[4,11–13] and evaluation of antepartum screening at 26 to 28 weeks gestation rather than 35 to 37 weeks gestation.[4,11,12] The effects of these deficiencies are not trivial. For example, arbitrarily chosen positive and negative predictive values for antepartum screening cultures may reduce the implied maternal vaginal colonization rate at term from 18.6% at screening to 18.2% or 17.4% if screening is performed at 28 or 36 weeks, respectively,[4] or increase it from 15.0% at screening to 15.8% at term if screening is performed

at 26 to 28 weeks,[13] resulting in artifactual changes in the estimated effectiveness of prevention strategies ranging from overestimates of nearly 7% for strategies based on screening at 36 weeks[4] to underestimates of 5% for strategies based on screening at 26 to 28 weeks.[13] Previous analyses predicted the results of predetermined prevention strategies. This analysis takes a fundamentally different approach: decision analysis was used to design prevention strategies by identifying groups of patients who will obtain the greatest benefit from prophylactic interventions, ensuring that patients who are at low-risk and will obtain little benefit are not inadvertently included among those selected for prophylaxis.

Because the specific recommendations for prevention strategies shown in Table 5 are derived from the decision analysis model, their reliability depends on the validity of the model. For this analysis, we developed a method for allocation of risk among population subgroups based on multiple identified risk factors.[30] The algorithm assumes that risk factors are statistically independent, which is reasonable for this particular analysis, in that Boyer and Gotoff[35] observed no correlation between GBS colonization status and intrapartum risk factors, GBS colonization does not change in prevalence during gestation[36–38] or correlate with an increased risk of prematurity,[39–41] and no data suggest covariance of the prevalence of PROM or intrapartum fever with length of gestation. Epidemiologic parameters included in the model represent the best estimates available from a detailed literature review,[18,19] and sensitivity analysis demonstrated that the implications of the model are not changed by variation in these parameters within the range of expected values. Furthermore, predictions of the model are consistent with clinical experience. For example, our risk allocation model predicts that 67.1% of infants with EOGBS will be premature or have intrapartum risk factors in the absence of any prophylaxis. This is consistent with empiric observations of Bosch Mestres et al[42] and Rosenstein et al[43] that preterm delivery, intrapartum fever, or prolonged rupture of membranes were present in 62% and 54% of cases of EOGBS disease, respectively, in populations in which some patients got intrapartum prophylaxis.

Comparisons between different methods of screening for GBS colonization depend heavily on estimates of the screening tests' performances. For example, if the predictive value of antepartum rectovaginal cultures for intrapartum vaginal cultures is overestimated or the sensitivity of the intrapartum screening test is underestimated, intrapartum screening would seem to be much better than, rather than nearly equivalent to, antepartum screening. Model parameters that apply to all strategies, such as the GBS colonization or attack rates, do not affect the relative effectiveness of different prevention schemes, but may alter quantitative implications of the model, potentially moving risk groups across a threshold for inclusion in the prophylaxis group. In populations with very low GBS attack rates, the estimated cost per case prevented would be correspondingly less favorable. Regional variations in the rates of GBS colonization or EOGBS disease may require careful consideration as individual facilities select prevention strategies.

Because of the methodological differences discussed above, we did not attempt detailed comparison of the predictions of our model with those of previous analyses. However, our results are concordant with those of Rouse et al[4] that screening at 26 to 28 weeks and treating colonized women with intrapartum risk factors (as proposed by the AAP in 1992[31]) is the least effective and most expensive strategy, the risk factor-based approach advocated by ACOG[5] and offered as an alternative by the CDC[1] is the least expensive, and prophylaxis based on screening at 35 to 37 weeks in accordance with CDC recommendations[1] is the most effective of the previously suggested regimens (Table 3). Reductions in EOGBS attack rates predicted by our analysis for the 1992 AAP (32.9%), 1992 ACOG (53.8%), and 1996 CDC (75.1%) strategies are lower than previous estimates[4] (50.7%, 68.8%, and 86.0%, respectively),[1] but similar to estimates of 78% for the screening-based strategy and 41% for the risk-based strategy obtained from a recent multistate surveillance study.[43] Our model estimates that the strategy proposed by Gotoff and Boyer[6] would be as effective as the antepartum screening strategy recommended by the CDC (Table 3). The latter approach relies heavily on use of postpartum prophylaxis, which is associated with increased mortality,[7,19] so this approach to prevention of GBS disease is best avoided.

None of the previously recommended strategies is the most effective possibility, because our decision analysis identified more effective strategies based on either screening cultures at 35 to 37 weeks or on intrapartum screening with the Strep B OIA. The primary reason for enhanced performance of these alternative strategies is integration of interventions for mothers and infants in a coordinated obstetrical and pediatric prevention effort, providing combined prophylaxis for a few high-risk neonates rather than intrapartum prophylaxis in a larger group of low-risk mothers. An integrated strategy based on antepartum screening, for example, adds treatment for 3.1% of neonates (with no increase in total antibiotic exposure) but reduces intrapartum prophylaxis from 30.7% to 24.7% of women and increases the number of cases prevented from 75.1% to 78.4%.

Risk-based ascertainment of candidates for prophylaxis may also focus interventions differently. For example, the CDC recommends intrapartum prophylaxis for all women with intrapartum risk factors, but this analysis suggests that this may not be necessary in women with negative antepartum rectovaginal cultures who deliver at term (Table 5). The major shortcoming of antepartum screening strategies are their inability to stratify risk in infants who deliver before screening. Use of a rapid screening test on all parturients on presentation for delivery does permit such risk stratification, as shown in Fig 1 and the Appendix. As a result, the strategy based on the Strep B OIA seems to be more effective, more efficient, and less costly than that based on rectovaginal cultures at 35 to 37 weeks (Table 5), requiring treatment of fewer women (24.2% vs 24.7%) and infants

(2.1% vs 3.1%) but preventing more EOGBS cases (80.1% vs 78.4%).

Estimates of total costs are heavily dependent on the estimated cost of screening and treatment. This analysis used cost estimates from a single source to minimize errors in cost comparisons. The cost estimate for screening cultures ($20) is the same as that used in several previous analyses,[9–11] but substantially below that used by Rouse et al[4] ($50). The cost of the Strep B OIA ($13), estimated using data from the manufacturer and laboratory personnel, is lower than that used by Rouse et al[4] ($30), but is in proportion to the cost difference between these models for screening cultures, and is lower than the cost estimate used by Yancey and Duff.[11] The estimated cost of maternal intrapartum antibiotic therapy ($29) is lower than that used by Yancey and Duff ($50)[11] or Mohle-Boetani et al[10] ($100) but almost identical with that used by Rouse and colleagues[4] ($30), and includes the distributed cost of treatment of allergic reactions, anaphylaxis, and maternal death. Previous studies did not consider costs of neonatal prophylaxis. Even if neonatal treatment were unnecessary, the CDC[1] recommends observation for at least 48 hours for all infants whose mothers were given intrapartum antibiotic prophylaxis, and notes that this "does not allow early discharge." Additional hospital days are costly,[44] so this recommendation has the potential to become very expensive as intrapartum prophylaxis is introduced for up to one-third of the population. There are other reasons to advocate a minimum of 48 hours of observation after birth, so allocation of this cost exclusively to GBS prevention is probably inappropriate. These potential costs are not considered in our model, but may be quite substantial, and may require consideration at centers with high early discharge rates. We also did not consider the costs of information systems that might be required to ensure that results of antepartum screening cultures, performed in obstetrical clinics, will always be available at the site and time of delivery. Even in a closed-panel health maintenance organization, in which the locations of prenatal care and delivery are closely linked and consistent, this expense may be substantial.

We did not attempt to estimate cost savings resulting from reduction in the GBS attack or mortality rates. GBS infection has a broad range of severity, from asymptomatic bacteremia easily treated with antibiotics to overwhelming pneumonia or septic shock requiring extracorporeal life support, and individual facilities may have skewed samples within this disease spectrum. Reliable estimates of average direct costs for treatment of a GBS case are therefore difficult, if not impossible, to establish. Actuarial estimates of the cost of treatment of EOGBS case in the range from $15 200 to $67 229.[9,10,45] Group B Strep Association members have self-reported an average cost of $65 000 per case.[33] It is not clear whether these estimates reflect costs incurred by or charged by the hospital, and the Group B Strep Association sample may be skewed by preferential inclusion of severe or fatal cases. Estimation of indirect and lifetime costs of GBS-related morbidity are similarly uncertain. We are unable to assign a monetary value to a neonatal death. We have therefore chosen to estimate only the direct costs per case averted.[11] Nonetheless, this analysis supports the conclusions of previous analyses that each of the prevention strategies evaluated does generate a net cost savings.[4,9,12,13] In this analysis, the cost of preventing one case of EOGBS using any of the strategies in Table 4 or either one recommended by the CDC is substantially less than the lowest of these estimates of the cost of managing a case of EOGBS ($15 200). Prevention would cost more than the higher estimates for treatment of cases ($67 229 per case) only if the cost estimates used in this model were increased at least eightfold. Because long-term and social costs of GBS disease are also ignored, arguments that GBS prevention programs are too expensive are not credible. This analysis does not address potential noneconomic or secondary costs of prevention strategies, such as the consequences of an increased prevalence of penicillin- or ampicillin-resistant GBS or enteric gram-negative organisms in the perinatal patient population.[46,47]

The decision analysis model presented here supports the belief that prevention strategies can effect a substantial reduction in the attack rate for EOGBS infections in neonates without excessive costs. However, complete eradication of this disease is impossible, and reduction in the EOGBS attack rate by 86% as suggested in the CDC recommendations would require treatment of a very large portion of the population (all women and 8.9% of infants for a risk factor-based strategy, 36.0% of women and 8.6% of infants for an antepartum screening strategy, or 25.8% of women and 23.5% of infants for an intrapartum screening strategy). Although the CDC recommendations create an imperative for use of some prevention strategy at all facilities that provide obstetrical services, there is no ethical, regulatory, medicolegal requirement that it be one of the CDC-recommended regimens. The strategies shown in Table 5 (except that based on a hypothetical test) provide potential alternatives. For these strategies, prophylaxis for infants is indicated primarily for those whose mothers have at least two risk factors, recapitulating the empirical observation that infection is much more likely (odds ratio = 8.5, $P < .001$) in infants with multiple as compared with a single maternal risk factor (preterm labor, intrapartum fever, or PROM).[48] Those based on risk factors only or on antepartum screening represent modest refinements of the strategies proposed by the CDC, in which the major change is explicit guidance for treatment of infants whose mothers received intrapartum antibiotics. Complicated protocols, such as the complex criteria for maternal and neonatal prophylaxis for an ideal intrapartum screening test (Table 5), or logistic barriers, such as the challenge of guaranteeing that antepartum screening test results are available at the time and place of delivery, may be important deterrents to successful implementation of a prevention strategy. Because the prophylaxis criteria are simplest for the strategy based on intrapartum screening (Table 5), this approach may be quite attractive. None of these prophylaxis regimens obviate the necessity for complete diagnostic evaluation and initiation of empiric intravenous antibiotic therapy in

very high risk infants born to women with a history of GBS bacteriuria during pregnancy, preterm premature rupture of membranes, or chorioamnionitis, or in infants who have a sibling or twin with EOGBS.

As new strategies are implemented, data on costs and outcomes should be systematically collected to guide iterative protocol refinements. Monitoring of mortality in addition to the EOGBS attack rate is essential to ensure that any reduction in adverse outcomes attributable to GBS infections is not accompanied by an equal or greater increase in morbidity or mortality from other causes. The recent CDC recommendations should not be viewed as the final statement on this important subject, but should provide the impetus for continued vigorous investigation and discussion as we

APPENDIX

Allocation of Risk for Neonatal Group B Streptococcal Sepsis—Effects of Gestational Age, Intrapartum Factors, and Maternal GBS Colonization

Risk Factors			Prevalence (%)	Attack Rate	GBS Cases in Category	
Maternal Screening for GBS Colonization	EGA (Weeks)	Fever or PROM			Per 1000 Total Births	% of Total GBS Cases
None	<28	Absent	0.74	0.0278	0.205	6.84
	<28	Present	0.06	0.2535	0.153	5.11
	28–30	Absent	0.83	0.0123	0.103	3.42
	28–30	Present	0.07	0.1294	0.088	2.93
	31–33	Absent	1.94	0.0056	0.109	3.63
	31–33	Present	0.16	0.0630	0.100	3.33
	34–36	Absent	6.01	0.0026	0.158	5.26
	34–36	Present	0.49	0.0304	0.149	4.97
	≥37	Absent	82.92	0.0012	0.987	32.91
	≥37	Present	6.78	0.0140	0.948	31.59
Rectovaginal culture at 35–37 weeks: Not done	<37	Absent	9.52	0.0060	0.575	19.16
	<37	Present	0.78	0.0630	0.490	16.34
Rectovaginal culture at 35–37 weeks: No GBS	≥37	Absent	64.04	0.0002	0.097	3.22
	≥37	Present	5.23	0.0018	0.097	3.23
Rectovaginal culture at 35–37 weeks: GBS +	≥37	Absent	18.88	0.0047	0.891	29.69
	≥37	Present	1.54	0.0551	0.851	28.36
Vaginal culture in labor: No GBS	<28	Absent	0.63	0.0002	0.001	0.05
	<28	Present	0.05	0.1259	0.065	2.17
	28–30	Absent	0.71	0.00009	0.001	0.02
	28–30	Present	0.06	0.0053	0.003	0.10
	31–33	Absent	1.66	0.00004	0.001	0.02
	31–33	Present	0.14	0.0007	0.001	0.03
	34–36	Absent	5.13	0.00002	0.001	0.03
	34–36	Present	0.42	0.0002	0.001	0.03
	≥37	Absent	70.74	0.00001	0.005	0.18
	≥37	Present	5.78	0.0001	0.005	0.19
Vaginal culture in labor: GBS +	<28	Absent	0.11	0.1877	0.204	6.79
	<28	Present	0.01	0.9935	0.088	2.94
	28–30	Absent	0.12	0.0835	0.102	3.40
	28–30	Present	0.01	0.8504	0.085	2.83
	31–33	Absent	0.29	0.0380	0.109	3.61
	31–33	Present	0.02	0.4248	0.094	3.30
	34–36	Absent	0.88	0.0178	0.157	5.23
	34–36	Present	0.07	0.2053	0.148	4.94
	≥37	Absent	12.18	0.0081	0.982	32.73
	≥37	Present	1.00	0.0947	0.942	31.40
Strep B OIA in labor: negative	<28	Absent	0.62	0.0081	0.050	1.67
	<28	Present	0.05	0.1526	0.077	2.56
	28–30	Absent	0.69	0.0034	0.024	0.79
	28–30	Present	0.06	0.0547	0.031	1.03
	31–33	Absent	1.62	0.0015	0.025	0.82
	31–33	Present	0.13	0.0210	0.028	0.92
	34–36	Absent	5.01	0.0007	0.035	1.18
	34–36	Present	0.41	0.0090	0.037	1.23
	≥37	Absent	69.17	0.0003	0.220	7.33
	≥37	Present	5.65	0.0039	0.221	7.35
Strep B OIA in labor: positive	<28	Absent	0.12	0.1264	0.155	5.17
	<28	Present	0.01	0.7608	0.076	2.54
	28–30	Absent	0.14	0.0572	0.079	2.63
	28–30	Present	0.01	0.5054	0.057	1.90
	31–33	Absent	0.32	0.0262	0.084	2.81
	31–33	Present	0.03	0.2743	0.072	2.41
	34–36	Absent	1.00	0.0123	0.122	4.08
	34–36	Present	0.08	0.1379	0.112	3.74
	≥37	Absent	13.75	0.0056	0.768	25.58
	≥37	Present	1.12	0.0647	0.727	24.24

Abbreviations: GBS, group B streptococcus; PROM, prolonged rupture of membranes.

seek the best method for prevention of neonatal GBS disease.

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