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## A POPULATION-BASED COMPARISON OF STRATEGIES TO PREVENT EARLY-ONSET GROUP B STREPTOCOCCAL DISEASE IN NEONATES

STEPHANIE J. SCHRAG, D.PHIL., ELIZABETH R. ZELL, M.STAT., RUTH LYNFIELD, M.D., AARON ROOME, PH.D.,  
KATHRYN E. ARNOLD, M.D., ALLEN S. CRAIG, M.D., LEE H. HARRISON, M.D., ARTHUR REINGOLD, M.D.,  
KAREN STEFONEK, R.N., M.P.H., GLENDA SMITH, B.S., MELANIE GAMBLE, M.P.H., AND ANNE SCHUCHAT, M.D.,  
FOR THE ACTIVE BACTERIAL CORE SURVEILLANCE TEAM

### ABSTRACT

**Background** Guidelines issued in 1996 in the United States recommend either screening of pregnant women for group B streptococcal colonization by means of cultures (screening approach) or assessing clinical risk factors (risk-based approach) to identify candidates for intrapartum antibiotic prophylaxis.

**Methods** In a multistate retrospective cohort study, we compared the effectiveness of the screening and risk-based approaches in preventing early-onset group B streptococcal disease (in infants less than seven days old). We studied a stratified random sample of the 629,912 live births in 1998 and 1999 in eight geographical areas where there was active surveillance for group B streptococcal infection, including all births in which the neonate had early-onset disease. Women with no documented culture for group B streptococcus were considered to have been cared for according to the risk-based approach.

**Results** We studied 5144 births, including 312 in which the newborn had early-onset group B streptococcal disease. Antenatal screening was documented for 52 percent of the mothers. The risk of early-onset disease was significantly lower among the infants of screened women than among those in the risk-based group (adjusted relative risk, 0.46; 95 percent confidence interval, 0.36 to 0.60). Because women whose providers had no strategy for prophylaxis may have been misclassified in the risk-based group, we excluded all women with risk factors and adequate time for prophylaxis who did not receive antibiotics. The adjusted relative risk of early-onset disease associated with the screening approach in this secondary analysis was similar — 0.48 (95 percent confidence interval, 0.37 to 0.63).

**Conclusions** Routine screening for group B streptococcus during pregnancy prevents more cases of early-onset disease than the risk-based approach. Recommendations that endorse both strategies as equivalent warrant reconsideration. (N Engl J Med 2002; 347:233-9.)

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THE use of intrapartum prophylaxis with antibiotics to prevent perinatal group B streptococcal infections has led to a 70 percent decline in the incidence of group B streptococcal disease during the past decade.<sup>1,2</sup> However, despite this dramatic decrease, early-onset group B streptococcal disease (in infants less than seven days old) remains a leading infectious cause of illness and death among newborns in the United States, resulting in approximately 1600 illnesses and 80 deaths annually.<sup>1</sup> Surviving infants may have long-term developmental disabilities, such as mental retardation or hearing or vision loss.

Current guidelines for prevention, issued in 1996 by the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and the Centers for Disease Control and Prevention (CDC), recommend that health care providers use either a risk-based or a screening approach to identify candidates for intrapartum antibiotic prophylaxis.<sup>3-5</sup> With the risk-based approach, women presenting at the time of labor with clinical risk factors for disease transmission (including fever, a prolonged interval between rupture of the membranes and delivery, or preterm delivery) are offered intrapartum antibiotic prophylaxis. With the screening approach, women are screened for carriage of group B streptococcus

From the Centers for Disease Control and Prevention, Atlanta (S.J.S., E.R.Z., M.G., A.S.); the Minnesota Department of Health, Minneapolis (R.L.); the Connecticut Department of Public Health, Hartford (A. Roome); the Georgia Department of Human Resources, Atlanta (K.E.A.); the Tennessee Department of Health, Nashville (A.S.C.); Johns Hopkins University Bloomberg School of Public Health, Baltimore (L.H.H.); the School of Public Health, University of California at Berkeley, Berkeley (A. Reingold); the Department of Human Services—Health Services, Portland, Ore. (K.S.); and the New York Department of Health, Albany (G.S.). Address reprint requests to Dr. Schrag at the Respiratory Diseases Branch, MS-C23, Division of Bacterial and Mycotic Disease, Centers for Disease Control and Prevention, 1600 Clifton Rd., Atlanta, GA 30333, or at zha6@cdc.gov.

between 35 and 37 weeks of gestation, and intrapartum chemoprophylaxis is offered to carriers. With both approaches, antibiotics are given during labor to women who had group B streptococcal bacteriuria during their current pregnancy, or who have previously had an infant with known group B streptococcal disease.

However, data are lacking on the relative effectiveness of these two strategies. Whereas population-based estimates of the proportion of infants with early-onset group B streptococcal disease who are born to mothers without clinical risk factors<sup>6</sup> suggested that the screening approach would lead to greater declines in the incidence of disease than the risk-based approach,<sup>6,7</sup> implementation of the risk-based approach is considered simpler than screening. Since 1996, both approaches have been recommended as equally acceptable, pending further data.<sup>3-5</sup>

We conducted a multistate, retrospective cohort study in a population of over 600,000 live-born infants to evaluate the effectiveness of the screening approach relative to the risk-based approach in preventing early-onset group B streptococcal disease.

## METHODS

### Population

Our target population consisted of infants born in 1998 and 1999 to residents of selected areas (see the Appendix) of the Active Bacterial Core Surveillance program of the Emerging Infections Program Network of the CDC.<sup>8</sup> Almost 100 percent of the hospitals that provide obstetrical services in these areas participate in the surveillance program. Only births that occurred in participating hospitals were included.

### Study Approval

The study protocol was approved by an institutional review board of the CDC, and a waiver of informed consent was granted. Appropriate local institutional review boards also reviewed the protocol and either approved it or determined that it was exempt from the requirement for approval.

### Sampling Design

A stratified random sample of births was drawn from birth-registry data. Strata were defined according to the surveillance area, the year, and the birth hospital. At least 500 births were selected per surveillance area to allow for accurate area-specific estimates. All surveillance-area hospitals with at least 10 births per year were included in the sampling frame. Within each stratum, births were sampled by proportional allocation; for small hospitals, at least 10 births that occurred during the two-year period were selected. All births of infants who had early-onset invasive infection were included in the sample. Invasive cases were defined by the isolation of group B streptococcus from a normally sterile site and were identified as part of routine population-based surveillance.<sup>8</sup>

Within strata, a constant statistical weight was assigned to each birth according to the inverse of its probability of selection; all births of infants with early-onset invasive infection were assigned a weight of 1 because all such births were included. Weights were adjusted to account for nonresponse (i.e., births without abstracted charts). The adjustment for nonresponse assumed that the births with abstracted charts within each stratum were representative of

the entire stratum. The weights within each surveillance area and birth year were further adjusted so that the total number of preterm births represented the number of preterm births in the overall population.<sup>9,10</sup>

### Data Collection

Trained abstracters reviewed the labor and delivery records for births in our sample using a standardized one-page form that included information on the following variables: demographic characteristics of the mother, adequacy of prenatal care, and the presence or absence of screening for group B streptococcus, clinical risk factors (i.e., gestation of less than 37 weeks, rupture of the membranes  $\geq$  18 hours before delivery, intrapartum temperature  $\geq$  38°C, group B streptococcal bacteriuria, previous infant with group B streptococcal disease), and intrapartum antibiotic use. In addition, data on the mother's race and ethnic background and the gestational age of the infant at birth (determined on the basis of the date of the last menstrual period) were collected from birth-registry files in each surveillance area. Abstracters were blinded to the disease status of the infant. For 21 cases of early-onset disease for which labor and delivery records were not available, we incorporated data on screening for group B streptococcus and intrapartum history collected as part of routine surveillance in the Active Bacterial Core Surveillance program.<sup>1</sup>

We assigned births to the screened or risk-based group using the following algorithm: any mother with documentation in the labor and delivery record (either in the admission record or in the prenatal records forwarded to the hospital) of a group B streptococcal culture performed at least two days before delivery was categorized in the screened group. All mothers without documentation of a test for group B streptococcus that adhered to the above criteria were categorized in the risk-based group. This categorization was based on the results of a recent national survey showing that 98 percent of obstetricians have a policy for the prevention of group B streptococcal disease that is a version of either the risk-based approach or the screening approach.<sup>11</sup>

### Definitions of Variables

Preterm delivery was defined as delivery at less than 37 weeks of estimated gestation. Intrapartum was defined as occurring during the period between the onset of labor or the rupture of the membranes and delivery. For infants delivered by cesarean section, intrapartum was defined as occurring during the period between admission for delivery and cord clamping. Adequacy of prenatal care was determined by the Kessner Index, which categorizes prenatal care as inadequate, intermediate, or adequate on the basis of the timing of the initiation of prenatal care, the gestational age at delivery, and the number of visits for prenatal care.<sup>12</sup> For univariate and multivariable models, we used only two categories: inadequate and not inadequate.

### Statistical Analysis

All analyses were conducted with the use of weights to account for unequal probability of selection. Data were analyzed with SUDAAN software (version 7.5.6, Research Triangle Institute) to account for the stratified survey design. Weighted values are reported.

The risk of early-onset disease in the screened group relative to the risk-based group was evaluated by univariate and multivariable models in which the disease status of the infant was the dependent variable. All variables that were associated with disease at a significance level of less than 0.15 in univariate models, as well as variables identified in previous studies as risk factors for early-onset disease, were considered in multivariable models with the use of PROC MULTLOG. The final multivariable model included main effects with a significance level of less than 0.05. All two-way interactions of main effects were evaluated. The efficacy of

intrapartum antibiotic prophylaxis (calculated as  $1 - \text{the relative risk}$ ) was evaluated in univariate models in which the disease status of the infant was the dependent variable and receipt of intrapartum antibiotics was the independent variable.

All P values are two-tailed. In multivariable analyses, odds ratios are assumed to approximate relative risks because early-onset disease was rare in this population.<sup>13</sup>

## RESULTS

### Population

We reviewed the labor and delivery records for 5144 live births randomly sampled from a total of 629,912 in the surveillance areas in 1998 and 1999. A total of 95 percent of the births selected for inclusion had abstracted charts (5144 of 5425). The gestational age for one infant in the risk-based group was not known; this birth was excluded from analyses because sample weights took into account gestational age. Active surveillance for early-onset group B streptococcal disease identified 312 cases in 1998 and 1999, for an overall incidence of 0.5 case per 1000 live births. All 312 births were included in our study.

Among the women whose newborns had early-onset disease, 62 percent (195 of 312) did not have evidence of clinical risk factors for transmission of group B streptococcal disease. In the population as a whole, 52 percent of the women were screened for group B streptococcus before delivery; the proportion of women who were screened varied geographically from 24 percent in selected counties in Oregon to 70 percent in Maryland.

Characteristics of the screened and risk-based groups are summarized in Table 1. The risk-based group included a significantly greater proportion of Hispanics than the screened group; the risk-based approach was more common in surveillance areas (California and Oregon) that included the majority of Hispanic women in our population. Overall, 98.1 percent of the women had at least one prenatal visit; however, women in the risk-based group were less likely to have had prenatal care and more likely to deliver before term than women in the screened group (Table 1). In contrast, the screened group included higher proportions of women with group B streptococcal bacteriuria during pregnancy and women who had previously had an infant with group B streptococcal disease.

### Factors Associated with Early-Onset Group B Streptococcal Disease

According to the univariate analysis, prenatal screening for group B streptococcus was associated with a lower risk of early-onset disease than was the risk-based approach (relative risk, 0.48; 95 percent confidence interval, 0.38 to 0.61) (Table 2). Intrapartum fever (temperature,  $\geq 38^\circ\text{C}$ ) and having previously had an infant with group B streptococcal disease

**TABLE 1.** CHARACTERISTICS OF THE WOMEN IN THE SCREENED AND RISK-BASED GROUPS.\*

CHARACTERISTIC	SCREENED GROUP (N=2628)	RISK-BASED GROUP (N=2515)	P VALUE
	percent		
Race			0.27
Black	22.5	22.2	
White	71.6	69.0	
Other	5.9	8.8	
Ethnic group			<0.001
Non-Hispanic	91.3	87.5	
Hispanic	8.7	12.5	
Age			0.39
<20 yr	7.6	8.4	
$\geq 20$ yr	92.4	91.6	
Prenatal care			
$\geq 1$ prenatal visit	99.4	97.1	<0.001
Prenatal record in chart†	97.6	92.7	<0.001
Adequacy of prenatal care†‡			<0.001
Inadequate	11.2	19.4	
Intermediate	28.7	33.9	
Adequate	60.1	46.7	
Medicaid payment of labor and delivery costs	24.7	25.5	0.52
Preterm delivery	7.1	14.0	<0.001
Membrane rupture $\geq 18$ hr before delivery	8.0	8.3	0.77
Intrapartum fever (temperature, $\geq 38^\circ\text{C}$ )	4.1	3.3	0.21
Group B streptococcal bacteriuria during pregnancy§	3.4	1.9	0.003
Previous infant with group B streptococcal disease	0.5	0.2	0.01

\*Reported values throughout take into account sample weights and the stratified survey design (see the Methods section).

†Percentages are of those women who received prenatal care.

‡Data are based on the Kessner Index,<sup>12</sup> which categorizes prenatal care into inadequate, intermediate, and adequate on the basis of the timing of the initiation of prenatal care, the infant's gestational age at delivery, and number of prenatal visits.

§Data are for the prevalence of documented group B streptococcal bacteriuria in the group as a whole; the denominator is not limited to women with documented urine tests.

were the factors associated with the highest risk of early-onset disease. Hispanic ethnic background was not associated with an elevated risk of early-onset disease. Similarly, group B streptococcal bacteriuria during pregnancy was not associated with an increased risk of early-onset disease; however, 82 percent of all women with group B streptococcal bacteriuria received intrapartum antibiotics.

Medicaid payment of costs for labor and delivery and inadequate prenatal care were predictors of early-onset group B streptococcal disease in the univariate, but not the multivariable, analyses (Table 2). In multivariable analyses, the screening approach remained associated with lower risk of early-onset disease relative to the risk-based approach (relative risk adjusted

**TABLE 2.** FACTORS ASSOCIATED WITH EARLY-ONSET GROUP B STREPTOCOCCAL DISEASE IN THE UNIVARIATE ANALYSIS.\*

CHARACTERISTIC	GROUP B STREPTOCOCCAL DISEASE (N=312)	NO GROUP B STREPTOCOCCAL DISEASE (N=4831)	RELATIVE RISK (95% CI)	
			UNIVARIATE MODEL	MULTIVARIABLE MODEL
		percent		
Screening for group B streptococcus before delivery	34.3	52.0	0.48 (0.38–0.61)	0.46 (0.36–0.60)
Medicaid payment of labor and delivery costs	33.3	25.1	1.49 (1.17–1.91)	
Group B streptococcal bacteriuria	4.2	2.5	1.69 (0.94–3.03)	
Preterm delivery (<37 wk)	17.0	10.4	1.76 (1.28–2.42)	1.50 (1.07–2.10)
Prolonged interval between membrane rupture and delivery ( $\geq$ 18 hr)	13.8	8.2	1.80 (1.28–2.53)	1.41 (0.97–2.06)
Inadequate prenatal care	24.4	15.2	1.80 (1.37–2.36)	
Black race	38.8	22.3	2.20 (1.73–2.80)	1.87 (1.45–2.43)
Maternal age <20 yr	18.6	8.0	2.64 (1.93–3.60)	2.22 (1.59–3.11)
Previous infant with group B streptococcal disease	1.3	0.3	3.79 (1.30–11.11)	5.54 (1.71–17.94)
Intrapartum fever (temperature, $\geq$ 38°C)	18.6	3.7	5.99 (4.28–8.38)	5.70 (3.94–8.23)

\*The multivariable model included only those main effects with a significance level of less than 0.05. Percentage values reported here take into account sample weights and the stratified survey design. CI denotes confidence interval.

for other factors in the multivariable model, 0.46; 95 percent confidence interval, 0.36 to 0.60) (Table 2).

#### Evaluation of Potential Confounders

Because preterm delivery was more common in the risk-based group and was associated with an increased risk of early-onset disease, we performed a stratified analysis limited to full-term births. Results were similar to those in Table 2, and the protective effect of screening relative to the risk-based approach remained significant (adjusted relative risk, 0.44; 95 percent confidence interval, 0.33 to 0.58).

Similarly, because it is recommended that prenatal screening be performed at 35 to 37 weeks of gestation and prenatal charts may be forwarded to hospitals before this time, we performed a subgroup analysis including women whose prenatal records were forwarded after 37 weeks of gestation (accounting for 38 percent of births). In this subgroup, screening remained associated with a lower risk of early-onset disease (adjusted relative risk, 0.32; 95 percent confidence interval, 0.21 to 0.49).

Another concern is that women whose providers had no strategy for preventing group B streptococcal disease may have been misclassified in the risk-based group. We therefore excluded from this group all women with risk factors who did not receive intrapartum antibiotics and who were in the hospital for at least two hours before delivery, allowing for time for intervention. When the observations for these 207 women (30 of whom had infants with early-onset group B streptococcal disease) were excluded,

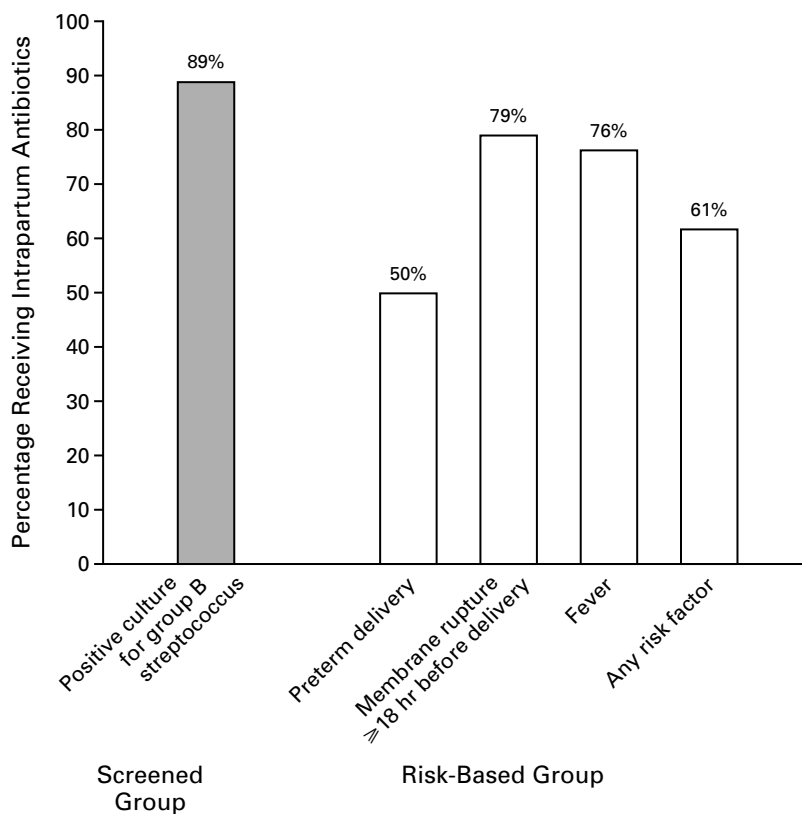
the risk of early-onset disease remained lower in the screened group (adjusted relative risk, 0.48; 95 percent confidence interval, 0.37 to 0.63).

#### Factors Contributing to the Protective Effect of Screening

In the screened group, 416 women (weighted proportion, 18 percent) had a positive culture for group B streptococcus in the absence of fever, a prolonged interval between rupture of membranes and delivery ( $\geq$ 18 hours), or preterm delivery. The incidence of disease among the infants of culture-positive women without these risk factors who did not receive intrapartum chemoprophylaxis was 1.3 per 1000 live births (95 percent confidence interval, 0.3 to 2.8 per 1000). The efficacy of intrapartum antibiotics in preventing early-onset group B streptococcal disease in the infants of culture-positive women without clinical risk factors was high — 88.6 percent (95 percent confidence interval, 66.4 to 96.1 percent).

Women in the screened group who had indications for prophylaxis were also significantly more likely to receive intrapartum antibiotics than those in the risk-based group (89 percent vs. 61 percent,  $P<0.001$ ) (Fig. 1). The median interval between admission and delivery did not differ between groups (screened group, 7.9 hours; interquartile range, 3.8 to 13.7; risk-based group, 7.2 hours; interquartile range, 3.2 to 13.4). The median interval between the identification of a clinical risk factor and delivery among women with risk factors in the risk-based group was 10.6 hours (interquartile range, 4.5 to 23.4).

We projected the effect of improved implementa-



**Figure 1.** Proportion of Women in the Screened Group and the Risk-Based Group with Indications for Chemoprophylaxis Who Received Intrapartum Antibiotics.

Preterm delivery was defined as delivery at less than 37 weeks of gestation. Fever was defined as an intrapartum temperature of 38°C or higher. "Any risk factor" includes group B streptococcal bacteriuria during the current pregnancy and having previously had an infant with group B streptococcal disease.

tion of the risk-based approach by assuming that all women in the risk-based group who had clinical risk factors but did not receive prophylaxis had actually received intrapartum antibiotics and that the efficacy of prophylaxis was 86 percent.<sup>14</sup> Under this assumption, the incidence of early-onset disease in the study surveillance areas would have decreased from 0.50 per 1000 live births to 0.44 per 1000 live births. This projected incidence, which assumes 100 percent compliance, remains higher than the observed incidence of early-onset disease among the infants of the screened women (0.32 per 1000 live births; 95 percent confidence interval, 0.26 to 0.38).

#### Anticipated Intrapartum Antibiotic Use under the Screening and Risk-Based Strategies

The proportion of deliveries to women colonized with group B streptococcus in the screened group (24 percent) did not differ from the proportion of

women with risk factors in the risk-based group (24 percent). In the screened group, culture-negative women with fever (accounting for 2 percent of deliveries) also received intrapartum antibiotics. An additional 5 percent of the women in each group received intrapartum antibiotics that were most likely not given for prophylaxis against group B streptococcal disease; they did not have documented indications for prophylaxis. Thus, with perfect implementation of either preventive strategy, the anticipated overall rate of intrapartum antibiotic use would be similar (31 percent in the screened group, 29 percent in the risk-based group).

#### DISCUSSION

Although the guidelines for the prevention of perinatal group B streptococcal disease that were issued in the United States in 1996 recommend the risk-based and screening approaches as equally acceptable,

debate continues over whether both strategies are equally effective. Although there are now observational data suggesting that each strategy can reduce the incidence of early-onset disease,<sup>14-18</sup> the strategies have not previously been directly compared. A series of single-hospital analyses<sup>19-22</sup> have been limited by the sequential use of the strategies and the investigators' inability to control for potential confounders. By incorporating data from multistate, population-based surveillance for early-onset disease into a sample survey of a population of over 600,000 live-born infants, we found that the screening approach was more than 50 percent more effective than the risk-based approach at preventing perinatal group B streptococcal disease.

The protective effect of the screening approach persisted when we controlled for recognized risk factors for early-onset disease.<sup>23-25</sup> The protective effect of the screening approach also persisted when we controlled for factors such as prenatal care or preterm delivery that differed between groups, most likely because we assigned women with no documented culture to the risk-based group. Furthermore, because the effectiveness of screening was based on actual implementation of this strategy in the field, it is possible that improved compliance with recommendations for culture collection and processing will result in further benefits.

The protective effect of screening stemmed from two main factors. First, by identifying women colonized with group B streptococcus who did not present with clinical risk factors, screening achieved a higher degree of coverage of the at-risk population than the risk-based approach. In the screened group, 18 percent of all deliveries were to culture-positive women without risk factors. The incidence of disease among infants of culture-positive women without risk factors who did not receive intrapartum prophylaxis was 1.3 per 1000 live births; in the era before prevention, the incidence of disease among such infants was as high as 5.1 per 1000 live births.<sup>26</sup> The efficacy of intrapartum antibiotics in preventing early-onset disease among infants of culture-positive women without risk factors was also close to 90 percent.

Women in the screened group who were culture-positive were also more likely to receive intrapartum antibiotics than women with clinical risk factors in the risk-based group. This difference was not explained by a greater opportunity to administer chemoprophylaxis in the screened group; the interval between the first appearance of a clinical risk factor and delivery in the risk-based group was greater than the median interval between admission and delivery in the screened group.

It is possible that the lower rate of use of intrapar-

tum antibiotics in the risk-based group reflects the inclusion in this group of some women whose providers had no strategy for prevention. However, the proportion of women in the risk-based group who received intrapartum antibiotics<sup>15</sup> was similar to that reported in the literature for institutions implementing the risk-based approach. In addition, even perfect implementation of the risk-based approach is not likely to lead to declines in the incidence of disease as great as those achieved with universal screening. This conclusion is supported both by a secondary analysis in which we excluded from the risk-based group all women with missed opportunities for prophylaxis and by projection of the incidence of disease in the risk-based group that would result from the provision of intrapartum antibiotics to all mothers of infants with early-onset disease who had had clinical risk factors but had not received intrapartum antibiotics.

The increased use of intrapartum chemoprophylaxis to prevent group B streptococcal disease has raised concern about potential adverse consequences of antibiotic use. However, our observation that anticipated intrapartum antibiotic use is similar with the two strategies suggests that the potential for adverse effects of chemoprophylaxis is also similar.

The absence of a significant association between group B streptococcal bacteriuria and early-onset disease that is reported here should not be taken as evidence that such bacteriuria is no longer an important indication for prophylaxis. Rather, we interpret this absence of association as evidence of successful prevention, since 82 percent of women with bacteriuria received intrapartum prophylaxis.

National policies for the prevention of group B streptococcal disease must take into account the effectiveness of different strategies, the risk of adverse or unintended consequences of preventive strategies, and the practical challenges involved in implementation. Our finding that screening was more effective than the risk-based approach in preventing early-onset disease in a large, multistate population suggests that a recommendation for universal screening warrants further consideration.

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## APPENDIX

Study locations included Maryland, 3 California counties (Alameda, Contra Costa, and San Francisco), 20 counties in the metropolitan area of Atlanta, 5 Tennessee counties (Davidson, Hamilton, Knox, Shelby, and Williamson), Connecticut, 3 Oregon counties (Clackamas, Multnomah, and Washington), 7 Minnesota counties (Anoka, Carver, Dakota, Hennepin, Ramsey, Scott, and Washington), and 7 New York counties (Genesee, Livingston, Monroe, Ontario, Orleans, Wayne, and Yates).

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