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# Trends in Incidence and Antimicrobial Resistance of Early-Onset Sepsis: Population-Based Surveillance in San Francisco and Atlanta

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**ABSTRACT.** *Objective.* Although increased use of intrapartum antibiotics caused significant declines in early-onset group B *Streptococcus* (GBS) infection, the effect on infections caused by other pathogens is not clear. The objective of this study was to determine trends in the incidence of early-onset sepsis caused by organisms other than group B streptococcus in the era of antimicrobial prophylaxis.

*Methods.* We conducted surveillance for early-onset sepsis as part of the Active Bacterial Core surveillance. A case was defined as isolation of bacteria from blood or cerebrospinal fluid from an infant who was 0 to 6 days of age and born in the surveillance area during 1998 through 2000 (248 184 births).

*Results.* We identified 408 cases of early-onset infection. GBS caused 166 (40.7%) cases (52 in 1998, 51 in 1999, and 63 in 2000 for incidences 0.62, 0.62, and 0.76 cases per 1000 live births, respectively). Other bacterial pathogens were identified in 242 cases (82 in 1998, 79 in 1999, and 81 in 2000 for incidences 0.99, 0.95, and 0.98 per 1000 live births, respectively) of early-onset sepsis. *Escherichia coli* caused 70 cases (0.25, 0.28, and 0.31 cases per 1000 live births, respectively, in 1998–2000). The proportion of *E coli* infections that were resistant to ampicillin increased significantly among preterm infants from 29% (2 of 7) in 1998 to 84% (16 of 18) in 2000 but not in full-term infants: 50% (4 of 8) in 1998 and 25% (1 of 4) in 2000.

*Conclusions.* Whereas rates of early-onset sepsis caused by GBS and other pathogens were low and did not change significantly during the study period, antibiotic-resistant *E coli* infections among preterm infants increased. Overall, these trends are reassuring, but careful evaluation of the increase in resistant infections in very young infants is critical in the future. *Pediatrics* 2002;110:690–695; *neonatal sepsis, group B Streptococcus,*

*guidelines, surveillance, Escherichia coli, antimicrobial resistance.*

ABBREVIATIONS. GBS, group B *Streptococcus*; CSF, cerebrospinal fluid.

Bacterial infection during the first 7 days of life, or early-onset infection, places an infant at risk for death or long-term disability.<sup>1–3</sup> Group B *Streptococcus* (GBS) is the leading cause of early-onset sepsis. Because intrapartum antibiotic prophylaxis has been shown to reduce early-onset GBS disease,<sup>4</sup> in 1996 consensus guidelines were issued recommending the use of intrapartum antibiotic prophylaxis for women who are at risk of transmitting GBS to their infants during labor.<sup>5–7</sup> Strategies were recommended to identify these women, and penicillin G, a narrow-spectrum antibiotic, was designated as the prophylaxis agent of choice. We estimate that the use of intrapartum antibiotics has doubled since the release of the consensus guidelines.<sup>8,9</sup> The Centers for Disease Control and Prevention's Active Bacterial Core surveillance has documented a 70% decline in the incidence of early-onset GBS disease from 1993 to 1999.<sup>10,11</sup> Although the decline in GBS disease has been attributed to the use of prophylactic antibiotics during labor, the effect of the increased use of intrapartum antibiotics on pathogens other than GBS that cause early-onset disease is unknown.

A few studies have evaluated trends in early-onset sepsis caused by organisms other than GBS.<sup>12–15</sup> Multicenter surveillance in Australia between 1991 and 1997 of >180 000 births compared infections in the first 48 hours of life caused by GBS with those caused by other organisms.<sup>15</sup> The incidence rates for early-onset disease caused by GBS and by other bacterial pathogens decreased significantly between 1991 and 1997. A second study, including nearly 47 000 births at a single hospital, looked at infection during the first week of life from 1991 to 1996.<sup>14</sup> The GBS infections decreased from 5 cases in 1991 to 1 case in 1996 at the hospital, whereas the number of infections caused by other organisms increased from 3 to 8 in the same time period. A study in Connecticut showed a decrease in GBS infections from 0.61/1000 in 1996 to 0.23/1000 in 1999, whereas non-GBS causes of infection did not change (0.65/1000 in 1996 and 0.68/1000 in 1999).<sup>16</sup> We conducted surveillance

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for early-onset sepsis in 2 metropolitan areas from 1998 through 2000 and compared the incidence of early-onset GBS infection with the incidence of infection from all other bacterial causes of early-onset disease.

## METHODS

To evaluate neonatal infections in a large population in which surveillance for early-onset GBS disease has been ongoing, the Active Bacterial Core surveillance, part of the Centers for Disease Control and Prevention's Emerging Infections Program Network, began conducting continuous, laboratory-based surveillance for early-onset neonatal sepsis in 1998. Surveillance was conducted in all hospitals with obstetric services in the 3-county San Francisco Bay area (1998 births: 39 768) and in 10 hospitals in the 8-county metropolitan Atlanta area (1998 births: 42 960). Surveillance officers in each region reviewed records from clinical microbiologic laboratories in their area on a regular basis. Duplicate records of cultures from the same infant were removed. A case was defined as isolation of a bacterial organism cultured from blood or cerebrospinal fluid (CSF) from an infant who was younger than 7 days and born in a hospital within the surveillance area. Surveillance officers collected on a standardized data collection form information regarding demographic characteristics, clinical outcome, and the isolate and its resistance profile. Additional information regarding maternal antibiotic exposure before and during labor was collected on infants with *Escherichia coli* infection. Isolates were defined as susceptible, intermediate, or resistant to various antimicrobial agents on the basis of the local laboratory's routine testing. Coagulase-negative staphylococci and other bacteria generally considered contaminants in this age group (corynebacterium, micrococcus, and diphtheroids) were excluded from the analysis. Cases of candidemia or other fungemia were not included in the surveillance, which focused on bacterial pathogens. Isolates from fetuses of <22 weeks' gestation were not included in the analysis. Birth data for each hospital in the surveillance area were obtained through the department of vital statistics in each state. All live births in the participating hospitals during 1998 were included in the denominators.

Statistical analysis was done using SAS<sup>17</sup> and EpiInfo version 6.<sup>18</sup> Incidence rates were calculated using 1998 hospital natality data. The  $\chi^2$  test or, when appropriate, Fisher exact test was used to evaluate differences in proportions.  $P < .05$  was considered statistically significant for all analyses.

## RESULTS

### GBS Versus All Other Causes of Early-Onset Infection

During 1998 through 2000, we identified a total of 408 cases of early-onset sepsis; 394 (96.6%) were identified in blood, 11 (2.6%) were identified in both blood and CSF, and 3 (0.7%) were identified in CSF alone. GBS accounted for 166 (40.7%), and *E coli* accounted for 70 (17.2%) of the cases detected (Table 1). Other common pathogens included viridans streptococci (16.5%), *Enterococcus* species (3.9%), and *Staphylococcus aureus* (3.7%). The majority of the early-onset meningitis cases were attributable to GBS (35.7% [5 of 14]), *E coli* (21.4% [3 of 14]), and group D *Streptococcus* (14.3% [2 of 14]).

Compared with infants with GBS infection, infants with early-onset infection caused by other organisms were more often born before 37 weeks' gestation (Table 2). Of the infants with known gestational age, 2 (16.7%) of 12 infants with meningitis were born before 37 weeks. Infants with early-onset sepsis caused by non-GBS bacteria were of lower birth weight than those with sepsis caused by GBS (Table 2). A fatal outcome was more likely in infants with other causes of infection compared with GBS (9.1% vs 3.1%;  $P = .03$ ). In the group with GBS infections, 4 (80%) of 5 of those who died were <37 weeks' gestation at birth versus 16 (76%) of 21 of those who died from other neonatal infection. Among preterm cases, GBS resulted in death in 11.5%, whereas other infections were fatal in 16.5% ( $P = .5$ , Fisher exact test). Among term cases, GBS and non-GBS infections were fatal in 1.5% and 3%, respectively ( $P = .7$ , Fisher exact test).

The day of illness onset differed between the GBS cases and cases with non-GBS causes of infection. More than 90% of the infections caused by GBS occurred within the first 48 hours of life, compared with <70% of the infections caused by other bacteria

**TABLE 1.** Bacteria Found to Cause Invasive Infection in Infants Younger Than 7 Days, Active Bacterial Core Surveillance, Selected Counties in California and Georgia, 1998–2000

Bacteria	No. of Total Isolates (N = 408)	Percentage of All Isolates	No. of CSF Isolates (N = 14)
GBS	166	40.7	5
<i>E coli</i>	70	17.2	3
Viridans streptococci	67	16.4	0
<i>Enterococcus</i> species	16	3.9	1
<i>Staphylococcus aureus</i>	15	3.7	1
Group D <i>Streptococcus</i>	12	2.9	2
<i>Pseudomonas</i> species	9	2.2	
<i>Streptococcus</i> not otherwise specified	9	2.2	
<i>Klebsiella</i> species	9	2.2	
<i>Haemophilus influenzae</i>	9	2.2	1
<i>Listeria monocytogenes</i>	6	1.5	
<i>Bacteroides fragilis</i>	5	1.2	
<i>Enterobacter cloacae</i>	4	1.0	1
<i>Streptococcus pneumoniae</i>	3	0.7	
<i>Peptostreptococcus</i>	2	0.5	
<i>Bacillus cereus</i>	2	0.5	
<i>Clostridium perfringens</i>	1	0.2	
<i>Proteus mirabilis</i>	1	0.2	
<i>Morganella morganii</i>	1	0.2	
<i>Yersinia enterocolitica</i>	1	0.2	

**TABLE 2.** Demographic Characteristics of Infants Younger Than 7 Days With Invasive Infection: GBS Versus All Other Causes of Bacterial Infection, Active Bacterial Core Surveillance, Selected Counties in California and Georgia, 1998–2000

Characteristic	Non-GBS (N = 242; %)	GBS (N = 166; %)	P Value
Male	53.7	53.6	.98
Race			
White	44.8	46.4	.33
Black	28.6	33.1	
All other	26.6	20.5	
Gestational age (wk)			
≥37	56.4	84.0	<.01
32–36	19.5	7.9	
<32	24.2	8.0	
Birth weight (g)			
≥2500	60.0	89.6	<.01
1500–2499	14.1	5.5	
<1500	25.9	4.9	
Fatal outcome	9.1	3.6	.03

(Fig 1). Eighteen percent of the infections caused by other pathogens had onset after the third day of life.

Between 1998 and 2000, the rates of early-onset GBS sepsis and sepsis caused by other pathogens varied by year in the 2 areas under surveillance (Table 3). Overall rates of GBS increased slightly during the 3 years of surveillance (0.13 cases per 1000 births) from 1998 to 2000, whereas infections caused by other pathogens did not change. In California, GBS incidence rates per 1000 births fluctuated during the study period with an overall increase of 62.5% in GBS incidence (0.25 cases per 1000) from 1998 to 2000. The incidence of sepsis caused by other pathogens increased in California, with a 39% overall increase from 1998 to 2000 and an absolute increase of 0.31 cases per 1000 births. In Georgia, the incidence rates for GBS remained stable, whereas other causes of early-onset sepsis decreased during the study period (by 32%) from 1998 to 2000.

#### Early-Onset *E coli* Infection

Seventy cases of *E coli* infection were identified during the 3-year period. The rates were similar in 1998, 1999, and 2000 at 0.25, 0.28, and 0.31 cases per 1000 births, respectively. Data concerning resistance to ampicillin were available for 57 (81%) of these cases (15 of 20 in 1998, 20 of 23 in 1999, and 22 of 27 in 2000); 37 of these were resistant to ampicillin and 20 were sensitive. The proportion of *E coli* infections with known susceptibility results that were resistant to ampicillin increased during the surveillance period, with 40% (6 of 15) ampicillin-resistant cases in 1998, 65% (14 of 20) in 1999, and 77% (17 of 22) in 2000 ( $P = .055$ ). Death occurred in 26% (5 of 26) of *E coli* cases caused by ampicillin-resistant organisms, compared with 4.7% (1 of 20) of *E coli* cases caused by ampicillin-sensitive *E coli* ( $P = .21$ , Fisher exact test).

Among the infants with *E coli* infections, 56 had known gestational age and ampicillin resistance data. Prematurity was evident in 78% of ampicillin-resistant infections and 47% of ampicillin-sensitive infections ( $P = .019$ ). Ampicillin resistance increased significantly among preterm cases of *E coli* infection

( $P = .004$ , linear trend; Fig 2A) but not among term cases ( $P = .71$ , linear trend; Fig 2B).

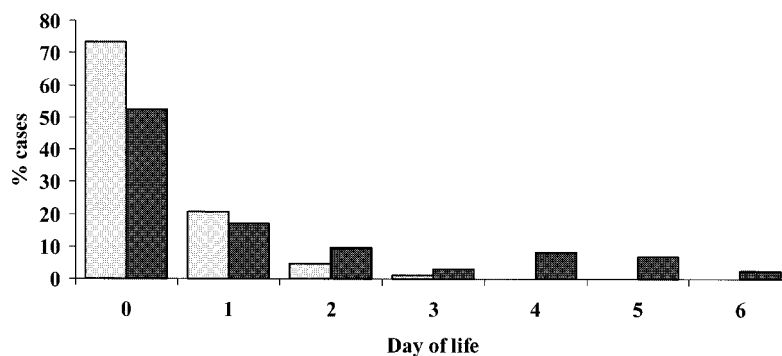
Exposure to maternal antibiotics before delivery (but after onset of labor and/or rupture of the membranes) was reported in 61% (43 of 70) of the infants with early-onset *E coli* infection. Of the 57 infected infants with available ampicillin susceptibility information, 70% (26 of 37) of those with ampicillin-resistant *E coli* infections and 40% (8 of 20) of the ampicillin-sensitive infections received antibiotics before delivery ( $P = .7$ ). Eighty-two percent (24 of 29) of the preterm infants who had ampicillin-resistant infections had maternal exposure to antibiotics compared with 56% (5 of 9) of the preterm infants with ampicillin-sensitive infections ( $P = .17$ , Fisher exact test). Among term infants, 40% (2 of 5) with ampicillin-resistant infection and 42% (6 of 14) of those with ampicillin-sensitive infection were exposed to maternal antibiotics before delivery ( $P = 1.0$ , Fisher exact test).

#### DISCUSSION

Overall from 1998 through 2000, the rate of early-onset sepsis caused by bacteria other than GBS was stable, with a modest decline in Atlanta and an increase in San Francisco. During the same period, we found a concerning increase in the number and proportion of ampicillin-resistant *E coli* infections. Ampicillin-resistant *E coli* infections occurred with increasing frequency among infants who were born prematurely, suggesting that differences in exposure to antibiotics between preterm and term deliveries may underlie this trend. Because we observed differences in the overall sepsis rates and trends between San Francisco and Atlanta, we are not able to generalize from the areas to the United States as a whole or to determine whether ampicillin-resistant *E coli* infections are increasing in other areas.

The use of intrapartum antibiotic prophylaxis has greatly reduced the occurrence of early-onset disease caused by GBS infection during the past decade.<sup>10</sup> With programs for GBS prevention in place, the incidence of early-onset GBS infections in several areas is approaching the Healthy People 2010 goal of 0.5 cases per 1000 live births,<sup>19</sup> but the effect, if any, that intrapartum antibiotic usage will have on other causes of neonatal sepsis has been of major interest. Our surveillance data do not resolve this issue, but they highlight the value of monitoring trends in diverse geographic locales over several years. A recent report from Connecticut during 1996 to 1999 found no increase in neonatal sepsis caused by non-GBS bacteria.<sup>16</sup> Both areas included in this surveillance experienced substantial decreases between 1993 and 1998 in rates of early-onset GBS sepsis (Table 3). Although we do not know the incidence of sepsis caused by pathogens other than GBS in San Francisco and Atlanta before 1997, the incidence measured from 1998 through 2000 is consistent with rates reported elsewhere.<sup>15,16,20</sup>

Consistent with previous studies comparing GBS and other causes of early-onset disease,<sup>20</sup> we found that infants who were infected with bacteria other than GBS were more likely to be born preterm and



**Fig 1.** Day of onset of infection in infants <7 days of age caused by GBS and by all other bacterial pathogens. Active Bacterial Core surveillance, selected counties in California and Georgia, 1998 to 2000. GBS is represented by the light bars, and non-GBS organisms are represented by the dark bars.

**TABLE 3.** Incidence Rates of Infection in Infants Younger Than 7 Days Caused by GBS and by All Other Bacterial Pathogens: Active Bacterial Core Surveillance, Selected Counties in California and Georgia, 1993, 1998–2000

Area	Complete ABCs Surveillance Areas in GA and CA*		Current Study (10 Hospitals in GA, All Births in Hospitals in the 3-County SF Bay Area)		
	1993*	1998*	1998	1999	2000
Georgia					
GBS	2.1	0.89	0.84	0.86	0.86
Non-GBS			1.2	0.81	0.86
California					
GBS	1.3	0.3	0.4	0.35	0.65
Non-GBS			0.80	1.10	1.11
Overall					
GBS			0.63	0.62	0.76
Non-GBS			0.99	0.95	0.98

\* Complete ABCs in 1993 and 1998 involved ascertainment of cases and births among residents of an 8-county surveillance area in metropolitan Atlanta and the 3-county San Francisco Bay area. Current study was limited to cases and births that occurred at 10 hospitals within Atlanta, Georgia, and all hospitals in the 3-county SF bay area and was not restricted to residents.

with low birth weight, although those conditions were present in a minority of infants. Death was also more common among the infants who were infected with bacteria other than GBS and was more common among preterm infants. Prematurity seems to account for the differences in survival between the groups rather than organism virulence.

GBS and *E coli* have been recognized as the leading causes of early-onset infection previously.<sup>20,21</sup> The most common pathogens that cause meningitis (GBS, *E coli*, and group D *Streptococcus*) were the most common causes of sepsis as well. Certain pathogens, such as *Haemophilus influenzae* and *Listeria monocytogenes*, have been well-known causes of neonatal disease in the past<sup>22,23</sup> but were not major causes of disease in the population that we studied. Few early-onset cases of meningitis were documented among the study population; meningitis accounts for a larger proportion of late-onset invasive infections caused by GBS, and the pattern may apply to other pathogens as well. As the incidence of GBS disease declines, tracking of the spectrum of organisms that cause early-onset disease will be critical to understanding a possible unintended consequence of intrapartum antibiotic prophylaxis for the prevention of GBS.

*E coli* was the second most common cause of neo-

natal infection in our study. One previous study found that the proportion of ampicillin-resistant *E coli* infections increased after institution of intrapartum GBS antibiotic prophylaxis with ampicillin in a single hospital.<sup>14</sup> In our study, we also found an increase in the proportion of ampicillin-resistant *E coli* infections; this trend reached statistical significance only among the premature infants. Among term infants, the proportion of ampicillin-resistant *E coli* infections did not change. There was no difference, however, of exposure to maternal antibiotics before delivery among the infants with ampicillin-resistant and ampicillin-sensitive infections. The increasing trend of ampicillin resistance among *E coli* infections in preterm infants may be attributable to several factors. Maternal exposure to antibiotics may select for resistant organisms and contribute to the overall trend. More likely, though, increasing antibiotic resistance in this population may be a reflection of overall trends for antibiotic resistance in community-acquired *E coli* infections. Recent studies report increasing ampicillin resistance in urinary tract infections caused by *E coli*<sup>24,25</sup> as well as increasing resistance in the hospital setting.<sup>26,27</sup> Premature infants may also be at higher risk for continuous exposure to maternal antibiotics, which may increase their

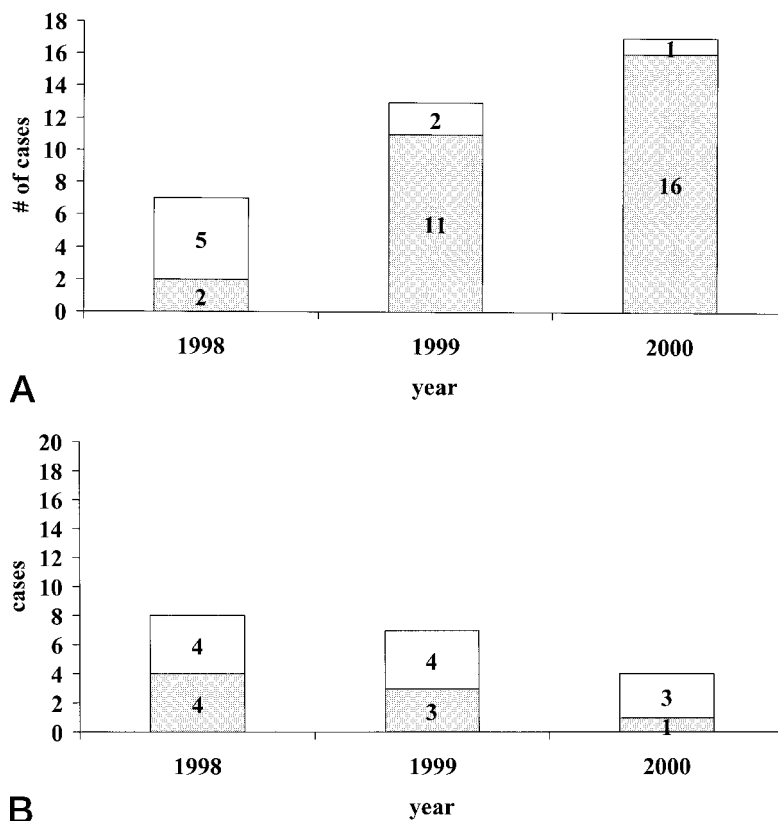


Fig 2. Ampicillin susceptibility in early-onset infection caused by *E coli* among preterm (gestation <37 weeks) infants ( $n = 37$  with available resistance data,  $P = .02$ , linear trend; A) and term ( $\geq 37$  weeks) infants ( $n = 20$  with available resistance data,  $P = .52$ , linear trend; B). Active Bacterial Core surveillance, selected counties in California and Georgia, 1998 to 2000. The shaded area of each bar indicates ampicillin-resistant *E coli* infection; the white area, ampicillin-sensitive *E coli* infection.

chance of selection for an antibiotic-resistant pathogen.

Antibiotics administered during labor may select for resistance among those organisms that colonize mothers or their newborns. Penicillin G has been the recommended agent for GBS prevention because of its efficacy against GBS as well as its narrow spectrum. Thus far, high-level penicillin resistance in GBS isolates has not been detected.<sup>28</sup> Penicillin is not, however, effective against most Gram-negative organisms that cause neonatal sepsis, such as *E coli*. Ampicillin was the prophylactic agent used by practitioners in the California hospital in which ampicillin-resistant *E coli* infections increased while GBS cases declined.<sup>14</sup> Ampicillin was also used in Australian hospitals, where infection caused by other organisms declined in parallel with declines in GBS infection.<sup>15</sup> Two recent large, randomized, controlled trials of oral amoxicillin-clavulanate for preterm prelabor rupture of membranes and preterm labor found no benefit against a composite morbidity outcome but identified an increase in necrotizing enterocolitis among infants in the amoxicillin-clavulanate group.<sup>29,30</sup> Risks of broad-spectrum  $\beta$ -lactam agents administered intrapartum may outweigh possible benefits in women without signs of infection. The use of the recommended penicillin over the broader spectrum ampicillin as intrapartum antibiotic prophylaxis to prevent early-onset disease should be emphasized to avoid any unnecessary selection pressure for antibiotic resistance.

There are certain limitations to our study. Data are available thus far for only 3 years. We therefore cannot determine long-term trends in infections caused by pathogens other than GBS. A second limitation is that the period under surveillance did not cover the period with the largest change in intrapartum antibiotic use. We cannot comment on whether there were overall trends in non-GBS sepsis cases as a result of the implementation of the GBS prevention guidelines. There may be misclassification of prepartum antibiotic exposure in infants whose mother received antibiotics that were not documented in the hospital chart. Because any outpatient antibiotics that the mother received have not been captured, our ability to assess the true impact of prepartum exposure to maternal antibiotics on antibiotic-resistant early-onset sepsis was limited. We had no information on antibiotic treatment in newborns, and some of the early-onset infections might represent nosocomial infections acquired in infants who were hospitalized for prematurity or other reasons. Because only 18% of non-GBS infections presented after the third day of life, the contribution of nosocomial infections to our sample likely is small. Another limitation is that although this was a population-based system, the surveillance areas may not be representative of the other US populations; our surveillance area represented 2.1% of the entire US birth cohort for 1998. As is suggested by geographic differences among the 2 areas in our study, substantial geo-

graphic variation in neonatal sepsis may occur in the United States.

The declining incidence of early-onset GBS disease during the past several years is attributable to the increased use of prophylactic intrapartum antibiotics. Our preliminary results concerning surveillance for other bacterial causes of neonatal sepsis are reassuring in that the incidence has not increased significantly. It is too soon to tell whether the non-GBS infection rate will increase as the GBS infections rate decreases and, in particular, whether drug-resistant infections in very young infants will emerge as a widespread problem. Our recognition of a significant increase in ampicillin-resistant *E coli* among preterm infants in these 2 surveillance areas makes surveillance in other areas a priority. Although there are indications for intrapartum antibiotic use, including treating GBS-colonized mothers to prevent infection in their infants, reducing unnecessary use and continuing surveillance for neonatal sepsis will be critical to evaluate the effects of GBS prevention activities.

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