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The Burden of Invasive Early-Onset Neonatal Sepsis in the United States, 2005–2008

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Abstract

Background—Sepsis in the first 3 days of life is a leading cause of morbidity and mortality among infants. Group B *Streptococcus* (GBS), historically the primary cause of early-onset sepsis, has declined through widespread use of intrapartum chemoprophylaxis. We estimated the national burden of invasive early-onset sepsis (EOS) cases and deaths in the era of GBS prevention.

Methods—Population-based surveillance for invasive EOS was conducted in 4 of CDC's Active Bacterial Core surveillance (ABCs) sites from 2005–2008. We calculated incidence using state and national live birth files. Estimates of the national number of cases and deaths were calculated, standardizing by race and gestational age.

Results—ABCs identified 658 cases of EOS; 72 (10.9%) were fatal. Overall incidence remained stable during the three years (2005:0.77 cases/1,000 live births; 2008:0.76 cases/1,000 live births). GBS (~38%) was the most commonly reported pathogen followed by *Escherichia coli* (~24%). Black preterm infants had the highest incidence (5.14 cases/1,000 live births) and case fatality (24.4%). Non-black term infants had the lowest incidence (0.40 cases/1,000 live births) and case fatality (1.6%). The estimated national annual burden of EOS was approximately 3,320 cases (95% CI: 3,060–3,580) including 390 deaths (95% CI: 300–490). Among preterm infants, 1,570

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cases (95% CI: 1,400–1,770; 47.3% of the overall) and 360 deaths (95% CI: 280–460; 92.3% of the overall) occurred annually.

Conclusions—The burden of invasive early-onset sepsis remains substantial in the era of GBS prevention and disproportionately affects preterm and black infants. Identification of strategies to prevent preterm births is needed to reduce the neonatal sepsis burden.

Keywords

early-onset; neonatal sepsis; group B *Streptococcus*; disease burden

INTRODUCTION

In the United States (US), sepsis is among the top 10 causes of neonatal and infant death.¹ Sepsis in the first week of life, particularly the first 3 days of life (early-onset, EOS), is commonly characterized by bacteremia, pneumonia, and meningitis and can lead to death and hearing loss, seizures, and neurodevelopmental abnormalities or delays among survivors.² Most EOS infections are a result of vertical transmission of bacteria from colonized mothers to infants during the intrapartum period.

Group B *Streptococcus* (GBS) has been the leading cause of EOS in the US since the 1970s.³ National guidelines for intrapartum antibiotic prophylaxis to prevent early-onset GBS infections were first issued in 1996 and updated in 2002 to recommend late antenatal GBS screening for all pregnant women.^{4,5} Incidence of invasive early-onset GBS infection declined by greater than 80% from 1990–2008, coinciding with an uptake of widespread GBS prevention efforts in the US.^{6–8} However, the proportion of infants exposed to intrapartum antibiotics also increased to 32% in the era of universal screening,⁷ raising concerns about potential increases in incidence of neonatal sepsis caused by Gram negative organisms, in particular, antimicrobial resistant pathogens.⁹

We used data from an active, multi-site surveillance system to estimate the national burden of invasive neonatal EOS infections and deaths in the era of widespread GBS prevention; we also evaluated pathogen-specific contributions to the burden.

MATERIALS AND METHODS

Active Bacterial Core surveillance (ABCs), a component of the Centers for Disease Control and Prevention's (CDC) Emerging Infections Program (EIP), conducted active, population-based surveillance for infants with EOS. Cases were defined as infants ≤ 2 days of age (0–72 hours of life), >22 weeks gestation, with one or more bacterial organisms isolated from either blood or cerebrospinal fluid (CSF), and live birth at a hospital in California (3-county Bay area), Connecticut (statewide), Georgia (8-county metro Atlanta area), and Minnesota (statewide, surveillance started in 2006) during 2005–2008. The surveillance population included approximately 159,000 live births in 2005, and approximately 233,000 live births annually from 2006–2008. Organisms that we classified as possible contaminants, such as coagulase-negative staphylococci (CoNS), *Corynebacteria*, and diphtheroids, were excluded. Maternal and infant demographic and clinical information were abstracted from the labor and delivery and medical chart records using a standardized form. Isolates were not collected; however, antimicrobial susceptibility was abstracted from infant medical charts.

Preterm births were defined as births at less than 37 weeks' gestation; number of days of gestation was not collected. Two categories for race were used: black and non-black (which included white, Asian or Pacific Islander, and American Indian or Alaska Native). Outcome was based on the known status of the infant at hospital discharge; cause of death was not

collected. *E. coli* cases with missing susceptibility results were excluded from calculations of ampicillin-resistant *E. coli* incidence. Surveillance-area incidence was calculated using live birth data from state vital records as the denominator; 2007 data were used for 2008.

To estimate the number of EOS cases nationally, we applied race (black, non-black) and gestational age (preterm, term) specific incidence to the number of US live births, obtained from the National Center for Health Statistics (NCHS) Vital Stats online birth and population files.¹⁰ Preliminary denominators (98% complete) for 2007 were used for both 2007 and 2008. Missing race and gestational age for the numerator and live birth denominators were distributed according to those with known race and gestational age within the relevant surveillance area for each year. Confidence intervals (CI) around the standardized incidence rates, case fatality ratios, and burden estimates were calculated using a method derived from the gamma distribution.¹¹

We compared burden estimates based on ABCs to estimates based on data from the NICHD Neonatal Research Network's (NRN) independent, multi-site EOS surveillance study.^{12–15} For the NICHD NRN study, cases were defined as illness in infants of all gestational ages weighing >400 grams at birth with the isolation of a bacterial organism from blood or CSF culture obtained in the first 72 hours of life and birth in one of 16 academic centers (see “Appendix” at the end of the paper) during 2006–2008. The surveillance population included approximately 93,000 live births in 2006, and approximately 103,000 live births annually from 2007–2008. Stillborn infants and infants that died in the delivery room as well as possible contaminants, such as *Corynebacteria* and diphtheroids, were excluded. Neonates positive for CoNS were only included as cases if more than one culture was positive and if the infant was continued on antibiotic therapy for 5 or more days. However, to improve comparability with ABCs for this analysis we excluded all CoNS from estimates derived from the NRN data.

Incidence in the NICHD NRN system was calculated based on live births in participating hospitals; race and gestational age were not collected for this denominator. To compare burden estimates across systems, national EOS estimates based on ABCs were adjusted for gestational age only and those for the NICHD NRN were adjusted for birth weight category (401–1500g, 1501–2500g, and >2500g), for the years 2006–2008. All analyses were performed using the SAS[®] software system, Version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

From 2005–2008, 658 cases of invasive neonatal EOS disease were reported to ABCs; 10.9% were fatal (Table 1). The most commonly reported pathogens were GBS (37.8%), *E. coli* (24.2%), viridans Streptococci (17.9%), *Staphylococcus aureus* (4.0%), and *Haemophilus influenzae* (4.0%). Case fatality ranged from 24.5% for *E. coli* infections to 2.5% for infants with viridans Streptococci. Overall incidence was 0.77 cases per 1,000 live births (95% CI, 0.72–0.84). The annual incidence remained stable over time (2005: 0.77; 2006: 0.79; 2007: 0.75; 2008: 0.76).

Black preterm infants had the highest disease incidence (5.14 cases per 1,000 live births) and case fatality ratio (24.4%). Non-black term infants had the lowest incidence (0.40 cases per 1,000 live births) and case fatality ratio (1.6%). Among preterm infants, *E. coli* was the most common infection (1.18 cases per 1,000 live births) with the highest case fatality ratio (32.1%). Among term infants, the leading infection was GBS (0.22 cases per 1,000 live births). There were no deaths among term infants with GBS.

Of the 159 reported *E. coli* cases, 121 (76.1%) had known antimicrobial susceptibility results. Of those, 81 (66.9%) were ampicillin resistant. Additionally, among 26 reported *S.*

aureus cases, antimicrobial susceptibility results were recorded for 23 (88.5%). Of those, one case (4.3%) was methicillin-resistant *Staphylococcus aureus* (MRSA).

We estimate that 3,320 (95% CI: 3,060–3,580) cases of invasive early-onset neonatal sepsis, including 390 deaths (95% CI: 300–490), occurred annually in the U.S. during 2005–2008 (Table 2); 47.3% of cases and 92.3% of deaths occurred among preterm infants. *E. coli* was the leading preterm pathogen among the cases and deaths, including those associated with ampicillin resistant infections. Among black infants, an estimated 1,100 cases (95% CI: 970–1,250; 33.1% of the overall) and 160 deaths (95% CI: 110–220; 41.0% of the overall) occurred annually. GBS was the leading infection (490 cases, 95% CI: 400–590) but *E. coli* was the leading pathogen associated with fatal outcome (90 deaths, 95% CI: 50–130) among black infants.

The pathogen distribution and disease incidence from the NICHD NRN¹² was similar to that of ABCs (Table 1). The national estimate adjusted for birth weight based on the NRN (3,310 cases, 95% CI: 2,930–3,740) was similar to the national estimate adjusted for race and gestational age based on ABCs (Table 2) and to the national estimate adjusted only for gestational age based on ABCs (3,490 cases, 95% CI: 3,200–3,800). Similarly, the estimated number of deaths was comparable to the national estimate adjusted for race and gestational age and the national estimate adjusted for gestational age alone (ABCs: 440 deaths, 95% CI: 340–560; NRN: 370 deaths, 95% CI: 270–500). In both systems, GBS was associated with the most cases and *E. coli* with the most deaths.

DISCUSSION

We estimated approximately 3,300 invasive EOS cases and 390 deaths annually in the US in the era of widespread prophylaxis for GBS prevention; 1,600 cases occurred among preterm infants and 1,100 cases among black infants. Despite dramatic declines in invasive GBS disease incidence over the past 10 years, GBS continues to be the leading cause of invasive EOS, causing over one-third of cases. *E. coli* is the second most common etiology, with approximately two-thirds of isolates resistant to ampicillin. This is the first US population-based estimate of invasive EOS disease burden based on multi-state data. Culture-confirmed invasive bacterial EOS represents a small fraction of the full EOS burden. In a neonatal sepsis case-series, culture-confirmed bacterial sepsis typically represented approximately 5% of all clinically-suspected neonatal sepsis.¹⁶ While a portion of clinical sepsis diagnoses likely captures non-infectious syndromes such as complications of preterm birth or metabolic instability, the limited sensitivity of blood and CSF cultures, particularly in neonates where it may be difficult to collect adequate specimen volumes and mothers may have received intrapartum antibiotics, contributes importantly to culture negative results.

It is striking that despite strong implementation of universal GBS screening guidelines,⁷ GBS remains the leading contributor to the remaining invasive EOS burden. There is potentially scope for further early-onset GBS prevention, including improved administration of intrapartum antibiotics to women with threatened preterm delivery, and minimization of false negative antenatal GBS screens among women delivering at term through improved adherence to specimen collection and processing recommendations. Revised GBS prevention guidelines issued in 2010 provide updated guidance to facilitate prevention implementation.¹⁷ However, intrapartum prophylaxis based on universal GBS screening alone will not lead to elimination of early-onset GBS disease, and the U.S. incidence is now close to the minimum that can likely be achieved under this strategy.¹⁸ Until alternative strategies, such as a GBS vaccine,¹⁹ become available, this burden will likely persist.

E. coli was a predominant early-onset neonatal pathogen before GBS emerged in the US and now that GBS incidence has declined, it again represents an important portion of EOS, particularly among preterm infants.^{12–15} Currently, there is no prevention strategy for *E. coli* EOS. Intrapartum antibiotic prophylaxis for GBS neither prevents nor increases the risk of *E. coli* EOS.²⁰ However, since beta-lactams are the most widely used IAP agents and more than half of neonatal *E. coli* EOS cases are now caused by ampicillin resistant strains, it is possible that prophylaxis with a regimen that would suppress neonatal colonization by both ampicillin resistant *E. coli* and GBS might reduce rates of EOS. Because such a high portion of infants with *E. coli* are preterm and case fatality ratios are higher than for GBS which is predominantly a term pathogen, prevention strategies are needed.

Our comparison of burden estimates between ABCs and the NICHD NRN demonstrated that gestational age is a dominant risk factor that cannot be ignored in invasive EOS analyses. Our findings highlight the importance of standardizing by gestational age at a minimum when calculating the burden of disease for invasive EOS. The ABCs data also emphasize the importance of race. Black race has been previously identified as a risk factor for invasive EOS in the US; data from ABCs has shown a disparate disease burden in black infants.^{8,21–23} Although our surveillance data can identify and monitor racial differences, race is likely a surrogate for social determinants of health that contribute more broadly to disease disparities. Unfortunately, neither ABCs nor the NICHD NRN capture further relevant variables. However geocoding, an exploration into the census tract and social economic distribution, may be one feasible strategy for future exploration.²⁴

There are certain limitations to our study. First, the ABCs EOS surveillance population is limited to 4 geographic areas which account for 5% of US live births. In this regard, it is reassuring that burden estimates based on ABCs and the NICHD NRN yielded similar results. However, both surveillance systems include mostly urban areas and may not accurately capture the pathogen incidence and distribution in more rural settings. Additionally, in the first days of life, it can be difficult to distinguish a sepsis-causing pathogen from a contaminant. We excluded all coagulase-negative staphylococci even though this organism has been associated with invasive disease. Similarly, in ABCs we included all viridians Streptococci even though in some instances these organisms may represent commensal flora. We have likely underestimated the true burden of disease caused by ampicillin resistant *E. coli*. Our burden estimates are based on approximately three-quarters of *E. coli* cases with recorded susceptibility data; we suspect the number of isolates actually resistant to ampicillin is greater and further strengthens the need for targeted prevention efforts. We are limited in stratifying our denominator more finely by gestational age beyond that of preterm and term. We expect preterm infants born very early to have a higher disease incidence and case fatality compared to those in the later stages of preterm; we would further expect this to differ by pathogen. Finally, because race and gestational age were the only variables available for denominator stratification in ABCs, we were not able to adjust for other variables when estimating the national burden.

GBS intrapartum prophylaxis has resulted in a notable reduction in the invasive EOS burden. However, the remaining EOS burden remains substantial, with both GBS and *E. coli* as important contributors. Exploration of pathogen-specific strategies to prevent *E. coli* infections holds promise as a way to further reduce the EOS burden. Additionally, identification and implementation of strategies to prevent preterm birth, such as prenatal care and risk directed interventions, would offer further hope for substantial reductions in EOS.

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Appendix. NICHD Neonatal Research Network (2006–2008)

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator) and Ms. Nellie Hansen (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Table 1

Invasive Early-Onset* Neonatal Sepsis Cases and Deaths, ABCs, 2005–2008

	Total		Black Preterm†		Black Term†		Non-Black Preterm†		Non-Black Term†	
	No. cases (Rate‡)	No. deaths (CFR§, %)	No. cases (Rate‡)	No. deaths (CFR§, %)	No. cases (Rate‡)	No. deaths (CFR§, %)	No. cases (Rate‡)	No. deaths (CFR§, %)	No. cases (Rate‡)	No. deaths (CFR§, %)
All years	658 (0.77)	72 (10.9)	131 (5.14)	32 (24.4)	120 (0.89)	2 (1.7)	158 (2.27)	34 (21.5)	249 (0.040)	4 (1.6)
2005¶	122 (0.77)	10 (8.2)	23 (4.25)	5 (21.7)	30 (1.07)	1 (3.3)	26 (2.00)	4 (15.4)	43 (0.38)	0 (0)
2006	185 (0.79)	20 (10.8)	30 (4.45)	10 (33.3)	39 (1.11)	1 (2.6)	47 (2.41)	8 (17.0)	69 (0.40)	1 (1.4)
2007	174 (0.75)	16 (9.2)	40 (6.01)	7 (17.5)	25 (0.69)	0 (0)	39 (2.11)	8 (20.5)	70 (0.41)	1 (1.4)
2008	177 (0.76)	26 (14.7)	38 (5.71)	10 (26.3)	26 (0.72)	0 (0)	46 (2.48)	14 (30.4)	67 (0.39)	2 (3.0)
Pathogen										
GBS	249 (0.29)	17 (6.8)	40 (1.57)	9 (22.5)	75 (0.55)	0 (0)	38 (0.55)	8 (21.1)	96 (0.15)	0 (0)
<i>Escherichia coli</i>	159 (0.19)	39 (24.5)	46 (1.81)	17 (37.0)	16 (0.12)	1 (6.3)	66 (0.95)	19 (28.8)	31 (0.05)	2 (6.5)
<i>E. coli</i> amp R¶¶	81 (0.09)	16 (19.8)	31 (1.22)	9 (29.0)	3 (0.02)	0 (0)	31 (0.45)	6 (19.4)	16 (0.03)	1 (6.3)
viridans Streptococci	118 (0.14)	3 (2.5)	16 (0.63)	2 (12.5)	16 (0.12)	0 (0)	18 (0.26)	0 (0)	68 (0.11)	1 (1.5)
<i>Staphylococcus aureus</i>	26 (0.03)	2 (7.7)	2 (0.08)	1 (50.0)	5 (0.04)	1 (20.0)	1 (0.01)	0 (0)	18 (0.03)	0 (0)
<i>Haemophilus influenzae</i>	26 (0.03)	4 (15.4)	10 (0.39)	1 (10.0)	0 (0)	0 (0)	12 (0.17)	3 (25.0)	4 (0.006)	0 (0)
Other**	80 (0.09)	7 (8.8)	17 (0.67)	2 (11.8)	8 (0.06)	0 (0)	23 (0.33)	4 (17.4)	32 (0.05)	1 (3.1)

* Occurring in infants aged 0–2 days (0–72 hours of life)

† Preterm classified as infants born <37 weeks gestation; term infants born at ≥37 weeks gestation

‡ Per 1,000 live births

§ CFR: case fatality ratio

¶ Includes cases from CT and selected counties in CA and GA; statewide surveillance in MN began in 2006

¶¶ Amp: ampicillin, R: resistant; Antimicrobial susceptibility data was available for 121 (76%) of 159 *E. coli* cases; those with missing susceptibility information were excluded from incidence and case fatality ratio calculations of ampicillin resistant *E. coli*.** Other category (N=80) includes the following pathogens: *Enterococcus* (n=14), *Listeria monocytogenes* (n=9), *Streptococcus pneumoniae* (n=8), *Citrobacter koseri* (n=7), group D *Streptococcus* (n=7), *Klebsiella pneumoniae* (n=6), group A *Streptococcus* (n=3), *Streptococcus bovis* (n=3), *Streptococcus* not otherwise specified (n=3), *Bacteroides fragilis* (n=2), group G *Streptococcus* (n=2),

Peptostreptococcus (n=2), *Streptococcus* not group D (n=2), AND 1 each of the following: *Aerococcus viridans*, *Actinomyces*, *Clostridium septicum*, *Enterobacter aerogenes*, *Kingella denitrificans*, *Klebsiella ornithinolytic*, *Moraxella* species, *Pseudomonas aeruginosa*, *Pseudomonas oryzaehabitans*, *Pseudomonas stutzeri*, *Serratia marsescens*, *Shigella* species.

Table 2

Average Annual Estimated National Number of Cases and Deaths* Associated with Invasive Early-Onset Neonatal Sepsis Adjusted by Gestational Age and Race, United States, 2005–2008

	No. cases (95% CI)	No. deaths (95% CI)
Overall	3320 (3060–3580)	390 (300–490)
group B <i>Streptococcus</i>	1210 (1060–1370)	90 (50–150)
<i>Escherichia coli</i>	840 (710–980)	210 (150–290)
<i>E. coli</i> ampicillin resistant [†]	430 (340–530)	80 (50–140)
viridans <i>Streptococci</i> [‡]	590 (490–710)	20 (3–50)
<i>Staphylococcus aureus</i>	130 (80–190)	10 (2–40)
<i>Haemophilus influenzae</i>	140 (90–210)	20 (10–60)
Other	410 (330–520)	40 (20–80)
Gestational Age		
Preterm [‡]	1570 (1400–1770)	360 (280–460)
group B <i>Streptococcus</i>	420 (330–520)	90 (50–150)
<i>E. coli</i>	620 (510–740)	200 (140–270)
<i>E. coli</i> ampicillin resistant [†]	330 (260–430)	80 (40–130)
v. <i>Streptococci</i> [‡]	190 (130–270)	10 (2–40)
<i>S. aureus</i>	20 (4–50)	10 (1–30)
<i>H. influenzae</i>	120 (80–190)	20 (10–60)
Other	220 (160–300)	30 (10–80)
Term [‡]	1740 (1570–1930)	30 (10–60)
group B <i>Streptococcus</i>	790 (670–920)	0 (0–20)
<i>E. coli</i>	220 (160–300)	20 (3–40)
<i>E. coli</i> ampicillin resistant [†]	90 (60–150)	10 (1–30)
v. <i>Streptococci</i> [‡]	410 (330–510)	10 (1–30)
<i>S. aureus</i>	110 (70–170)	10 (1–30)
<i>H. influenzae</i>	20 (6–50)	0 (0–20)
Other	190 (140–260)	10 (1–30)
Race		
Black	1100 (970–1250)	160 (110–220)
group B <i>Streptococcus</i>	490 (400–590)	40 (20–80)
<i>E. coli</i>	280 (220–360)	90 (50–130)
<i>E. coli</i> ampicillin resistant [†]	160 (110–220)	40 (20–80)
v. <i>Streptococci</i> [‡]	140 (100–200)	10 (2–30)
<i>S. aureus</i>	30 (10–60)	10 (2–30)
<i>H. influenzae</i>	50 (20–90)	10 (1–30)
Other	110 (70–170)	10 (2–30)
Not-black	2220 (2000–2430)	230 (160–310)
group B <i>Streptococcus</i>	720 (600–850)	50 (20–100)

	No. cases (95% CI)	No. deaths (95% CI)
<i>E. coli</i>	560 (450–680)	130 (80–190)
<i>E. coli</i> ampicillin resistant [†]	270 (200–360)	40 (20–90)
v. Streptococci [‡]	450 (360–560)	10 (1–30)
<i>S. aureus</i>	100 (60–150)	0 (0–20)
<i>H. influenzae</i>	90 (50–150)	20 (4–50)
Other	300 (230–390)	30 (10–70)

* Incidence standardized by race and gestational age to the population of the U.S. using incidence from ABCs

[†] National estimates of ampicillin resistant *E. coli* cases are based on incidence from ABCs *E. coli* cases with known susceptibility results (121/159 or 76%).

[‡] Preterm classified as infants born <37 weeks gestation; term infants born at ≥37 weeks gestation

CI: confidence interval