Revisiting the Need for Vaccine Prevention of Late-Onset Neonatal Group B Streptococcal Disease

A Multistate, Population-Based Analysis

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Background: Intrapartum antibiotic prophylaxis for neonatal group B streptococcal disease (GBS) effectively prevents disease among infants <7 days old, but there are no prevention strategies for late-onset GBS disease (onset on days 7–89 of life). We describe trends in late-onset GBS over a 16-year period to characterize disease burden and estimate vaccine preventability.

Methods: We conducted active, population-based surveillance for invasive late-onset GBS disease in 10 states from 1990 to 2005. A case was defined by GBS isolation from a normally sterile site on day 7–89 of life in a surveillance area resident. Incidence rates were calculated per 1000 resident live births.

Results: We identified 1726 cases; 26% presented with meningitis, and the case fatality ratio was 4.3%. Incidence was similar throughout the study period. Incidence among black infants was approximately 3 times that among nonblack infants; the disparity persisted when data were stratified by gestational age. We estimate approximately 1300 cases of late-onset GBS occur annually in the United States. Birth at <37 weeks gestation was common among case-infants (49%) and was associated with elevated case fatality (relative risk: 3.8; 95% confidence interval: 1.1–13.2). Of 653 serotyped isolates, serotypes III (53%), IA (24%), and V (13%) predominated. During 2003–2005, 81 (36%) of the 227 cases caused by serotypes III, IA, and V were born before 34 weeks gestation.

Conclusions: The late-onset GBS disease burden remains substantial. A trivalent vaccine could be an effective prevention strategy. Because many cases were born preterm, reducing the opportunity for transplacental antibody transfer, adolescent immunization should be considered.

Key Words: group B streptococcus, neonatal, surveillance, vaccine

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When group B streptococci first emerged as a major cause of neonatal sepsis and death in the United States,[1–4] the incidence of disease was highest among infants in the first week of life (early-onset GBS disease).[5] National guidelines for early-onset GBS disease prevention, first issued in 1996[6] and updated in 2002,[7] were associated with a nearly 80% decline in the incidence of early-onset GBS disease in the United States[8,9]; meanwhile, the frequency of intrapartum antibiotic use rose to approximately 30% of deliveries.[10,11]

In contrast, there are no prevention strategies for GBS infection among infants with illness onset on day 7–89 of life (late-onset GBS disease). Although prematurity, black race, and maternal GBS colonization are known to increase the risk of late-onset GBS disease,[12,13] these risk factors have not led to the identification of interventions. A lack of understanding of the dominant modes of late-onset disease transmission further hinders efforts to develop prevention measures; fewer than half of infants with late-onset GBS disease are born to mothers with prenatal GBS colonization,[13] suggesting that direct

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vertical transmission is only partly responsible. Although case reports have implicated breast milk[14–18] and the hands of healthcare workers as sources of infection,[19–21] whether these are common routes of transmission is unknown.

Because vertical transmission likely contributes to late-onset GBS disease, it was hoped that intrapartum prophylaxis for early-onset GBS disease might also prevent some cases of late-onset disease. Previous evaluations of surveillance data[5,22] suggest this has not occurred, but the hypothesis has not been rigorously evaluated. Also unexplored are potential unintended consequences of widespread intrapartum antibiotic prophylaxis on late-onset disease. Theoretically, intrapartum antibiotics may delay GBS disease presentation, shifting disease onset into the period beyond the first week of life. Changes in the serotypes or antibiotic susceptibility of the organisms responsible for late-onset GBS disease could also have occurred, conceivably altering the severity of late-onset GBS disease.

To date, vaccination is the most promising strategy for late-onset GBS disease prevention[23]; serotype-specific capsular polysaccharide-conjugate vaccines currently hold the most potential, and common protein vaccines are also under development.[24,25] Proposed approaches include vaccination of adolescent girls or vaccination in the third trimester of pregnancy.[24] Trials of candidate vaccines have found that serum antibody concentrations peak 4–8 weeks after immunization, so the optimal timing for maternal vaccination would be early in the third trimester.[26,27] In a report on new vaccines for the 21st century, the Institute of Medicine identified a GBS vaccine for either pregnant women or adolescent girls as favorable compared with developmental vaccines against other infections.[28] The recent recommendation for use of the human papilloma virus vaccine among adolescent girls has led to strengthening of the adolescent immunization platform, paving the way for an adolescent GBS vaccination strategy.

To evaluate the impact of early-onset GBS prevention strategies on late-onset GBS disease and assess the potential for vaccine prevention of late-onset disease, we analyzed data from 16 years of multistate, population-based surveillance. We also described the recent epidemiology of late-onset GBS disease and estimated the current national burden of disease.

METHODS

Active Bacterial Core Surveillance. We conducted active, population- and laboratory-based surveillance for invasive GBS disease from 1990 to 2005 using previously described methods for the Emerging Infections Program.[29] Participating laboratories processed cultures for residents of the following areas: 3 California counties since 1990; 5 Colorado counties since 2001; Connecticut, statewide since 1996; 8 Georgia counties since 1990 and 12 additional counties since 1997; Maryland, statewide since 1992; 7 Minnesota counties since 1996 and statewide since 1999; New Mexico, statewide since 2004; 7 New York counties since 1998 and 8 additional counties since 1999; 3 Oregon counties since 1996; and 4 Tennessee counties since 1990, 1 additional county since 1995, and 6 additional since 2000. These areas had a total of 454,505 live births in 2004, 11% of live births in the United States.[30] The 2004 population under surveillance was 72% white, 18% black, and 9% other races; the full United States population in 2004 was 82% white, 13% black, and 5% other races.

A case of invasive GBS disease was defined by isolation of GBS from a normally sterile body site in a surveillance area resident less than 90 days of age. We excluded GBS cultures taken from amniotic fluid, placental products, or urine. Medical records were reviewed using a standardized case-report form, which was expanded to capture detailed prenatal, obstetric, and neonatal information in 2003.

Isolate Collection and Testing. Collection of GBS isolates for serotype characterization and antibiotic susceptibility testing was optional. Maryland and metropolitan Atlanta, Georgia collected isolates between 1992 and 1994. In 1996, Minnesota and Oregon began isolate collection, and the number of sites participating in isolate collection increased to 7 by 2005 (Colorado, Georgia, Maryland, Minnesota, New Mexico, New York, and Oregon). Isolates were serotyped by latex agglutination tests with rabbit antisera to GBS capsular polysaccharide types Ia, Ib, and II–VIII.[31] The Lancefield method was used when latex tests were indeterminate.[32] If both tests were indeterminate, the isolate was classified as nontypeable (NT). Isolate susceptibility to penicillin, ampicillin, cefazolin, erythromycin, clindamycin, and vancomycin was determined by broth dilution using interpretive standards established by the Clinical and Laboratory Standards Institute.[33]

Definitions. We considered cases with positive sterile-site cultures obtained on day 1 through 6 of life early-onset GBS disease and cases with positive cultures from day 7 to 89 of life late-onset GBS disease. Presenting clinical syndromes were defined based on discharge diagnosis recorded in the medical record. Additionally, all infants with CSF cultures positive for GBS were categorized as having meningitis. Infants with isolated bacteremia had GBS isolated from blood only and had no alternate syndrome recorded in the medical record. Late-onset GBS cases with a first positive GBS culture obtained 3 or more days after hospitalization were considered nosocomial. We defined prematurity as birth before 37 weeks of gestation. Low birth weight was defined as weight <2500 g; very low birth weight was defined as <1500 g. Race, as recorded in the medical record or, when missing, on the birth certificate, was categorized as black, white, or other, and ethnicity as Hispanic or non-Hispanic. Disease outcome was collected from the infant record and represents in-hospital death or survival to hospital discharge. In-hospital deaths were attributed to GBS disease. We considered 1990–1995 the period of limited neonatal GBS disease prevention, 1996–2002 the years of transition to widespread implementation of intrapartum antibiotic prophylaxis, and 2003–2005 the period of universal screening.

Analysis. For incidence rate calculations, numerators were the observed case counts from surveillance, and denominators the number of live births in the participating surveillance sites, obtained from state vital records.[30,34] Incidence for 2005 was calculated using 2004 live birth data. Trends in GBS disease incidence over time in consistently collecting areas alone did not differ importantly from trends identified in recently added surveillance areas, so data from all 10 collecting sites were combined for the analysis of trends over time.

For descriptive epidemiology, we limited analysis to data from 2003 to 2005, years for which enhanced maternal and labor and delivery data were available. Beginning in 1996, race was obtained from the birth certificate if missing from the prenatal chart. For incidence rate and burden of disease calculations, race was assigned using a multiple imputation method (described elsewhere[35]) if missing from both the prenatal chart and the birth certificate. To estimate the national burden of disease, we applied race-specific rates of invasive neonatal GBS disease identified through surveillance to U.S. population figures for each racial group. Analyses were conducted using SAS, version 9.1. Ninety-five percent confidence intervals are reported throughout. χ^2 tests were used to compare proportions, and a P value <0.05 was considered significant. The Kruskal-Wallis test was used to compare medians. Changes in incidence over time were analyzed using the χ^2 test for linear trend.

RESULTS

We identified 1726 cases of late-onset neonatal GBS disease between January 1990 and December 2005. Seventy-nine percent of isolates were obtained from blood, 19% from cerebrospinal fluid, 2% from synovial fluid, and <1% from other sites. Twenty-three (1%) episodes were polymicrobial; organisms identified in samples with GBS included enterococci, coagulase negative staphylococci, and *Staphylococcus aureus*. Approximately half (52%) of case-infants were male; 48% were black, 44% were white, 4% were of other races, and race was unknown for 4%.

Trends in Late-Onset GBS Disease. Between 1990 and 2005, the incidence of late-onset GBS disease ranged from as low as 0.29 to as high as 0.47/1000 live births annually (Fig. 1A). There was some year-to-year fluctuation but no marked change in the incidence of late-onset GBS disease during the study period; incidence was 0.41/1000 live births during the years of limited prevention (χ^2 for linear trend = 0.04; P = 0.85), 0.34/1000 during the transitional years (χ^2 for linear trend = 1.8; P = 0.18), and 0.35/1000 during the period of universal screening (χ^2 for linear trend = 1.3; P = 0.25). As shown previously,[8,9,23,30] the incidence of early-onset disease declined by 80% during this period (Fig. 1A). Because intrapartum antibiotics could conceivably have a greater effect on GBS disease within the first month of life than on disease later in infancy, we stratified late-onset GBS disease into 2 age groups: 7-29 days and 30-89 days of age at onset. The incidence of late-onset disease in each of these age groups was stable between 1990 and 2005 (Fig. 1B). Early-onset GBS disease was approximately 3 times as common as late-onset disease in the years of limited GBS prevention, but the incidences of early and late-onset GBS disease were similar during the period of universal screening (0.34/1000 and 0.35/1000, respectively).

The incidence of late-onset GBS disease in black infants was approximately 3-fold that in nonblack infants throughout the study period (Fig. 2, http://links.lww.com/A563). This disparity persisted when incidence was stratified by gestational age: full-term incidence from 2003 to 2005 was 0.42/1000 in black infants and 0.11/1000 in nonblack infants, whereas preterm incidence was 2.49/1000 in black infants and 1.03/1000 in nonblack infants. During 2002-2005, the incidence of late-onset GBS disease rose in black infants (χ^2 for linear trend = 4.6; P = 0.03) while remaining stable in nonblack infants (χ^2 for linear trend = 0.3; P = 0.58).

Late-onset GBS disease presented most often with isolated bacteremia (67%), followed by meningitis (26%), pneumonia (2%), cellulitis (2%), and septic arthritis (2%). The proportion of cases presenting with meningitis (range, 21–35%) did not increase during the study period (Table 1). Overall, the median age at onset of illness was 36 days, shifting from 32 days in the years of limited GBS disease prevention to 37 days during the transitional years and in the era of universal screening (Kruskal-Wallis χ^2 = 4.94; P = 0.08). Of 1692 cases with a known outcome of illness, 73 (4.3%) died; the case-fatality ratio was 4.3 in the years of limited GBS disease prevention, 4.8 in the transition years, and 3.5 in the era of universal screening. The case-fatality ratios associated with bacteremia, meningitis, and pneumonia were 3%, 6%, and 12%, respectively.

Descriptive Epidemiology, 2003–2005. Between 2003 and 2005, 468 cases of late-onset GBS disease occurred in the surveillance areas; enhanced prenatal, neonatal, and maternal data were available for 455 (97%). Characteristics of case-infants are shown in Table 2. One hundred twenty-five cases (27%) presented with meningitis. GBS was isolated from cerebrospinal fluid (CSF) and blood in 37% of these cases, from blood alone in 35%, and from CSF alone in 28%. Of the 222 case-infants (49% of 455) born preterm, the median gestational age was 30 weeks (interquartile range, 27–34 weeks).

The median maternal age was 25 years. Maternal prenatal GBS screening was documented for 182 (40%) cases. Of the 273 cases with no or unknown maternal screening status, 187 (69%) were born preterm. Eighty-three (46%) mothers with documented prenatal screening were positive for GBS colonization. Nearly half of case-infants (47%) were exposed to intrapartum antibiotics, most often for GBS prophylaxis (56%), caesarian section prophylaxis (6%), or suspected chorioamnionitis (6%).

In 127 cases (28%), GBS was isolated at least 3 days after hospital admission; the median age at the time of nosocomial GBS onset was 38 days (interquartile range, 21–54 days). Nearly all (n = 121, 95%) of the nosocomial cases occurred in preterm infants (median gestational age, 28 weeks), 110 of whom remained hospitalized between birth and the onset of GBS disease. The median duration of hospitalization was 10 days (intraquartile range, 6–14 days) among non-nosocomial cases (n = 304), and 73 days (interquartile range, 49–92 days) among nosocomial cases.

We examined characteristics associated with death for 453 cases with a known outcome of illness (Table 3). Preterm birth [relative risk (RR): 3.8; 95% confidence interval (CI): 1.1–13.2] and very low birth weight (RR: 5.8; 95% CI: 1.9–18.1) were associated with an elevated risk of death. The case fatality ratio was 1% in full-term infants, 3% in infants with a gestational age of 29–36 weeks, and 8% in infants born at <29 weeks gestational age (P = 0.005 for linear trend). Infants with very low birth weight had a case fatality ratio of 8%, compared with 2% in infants with normal birth weight (P = 0.005).

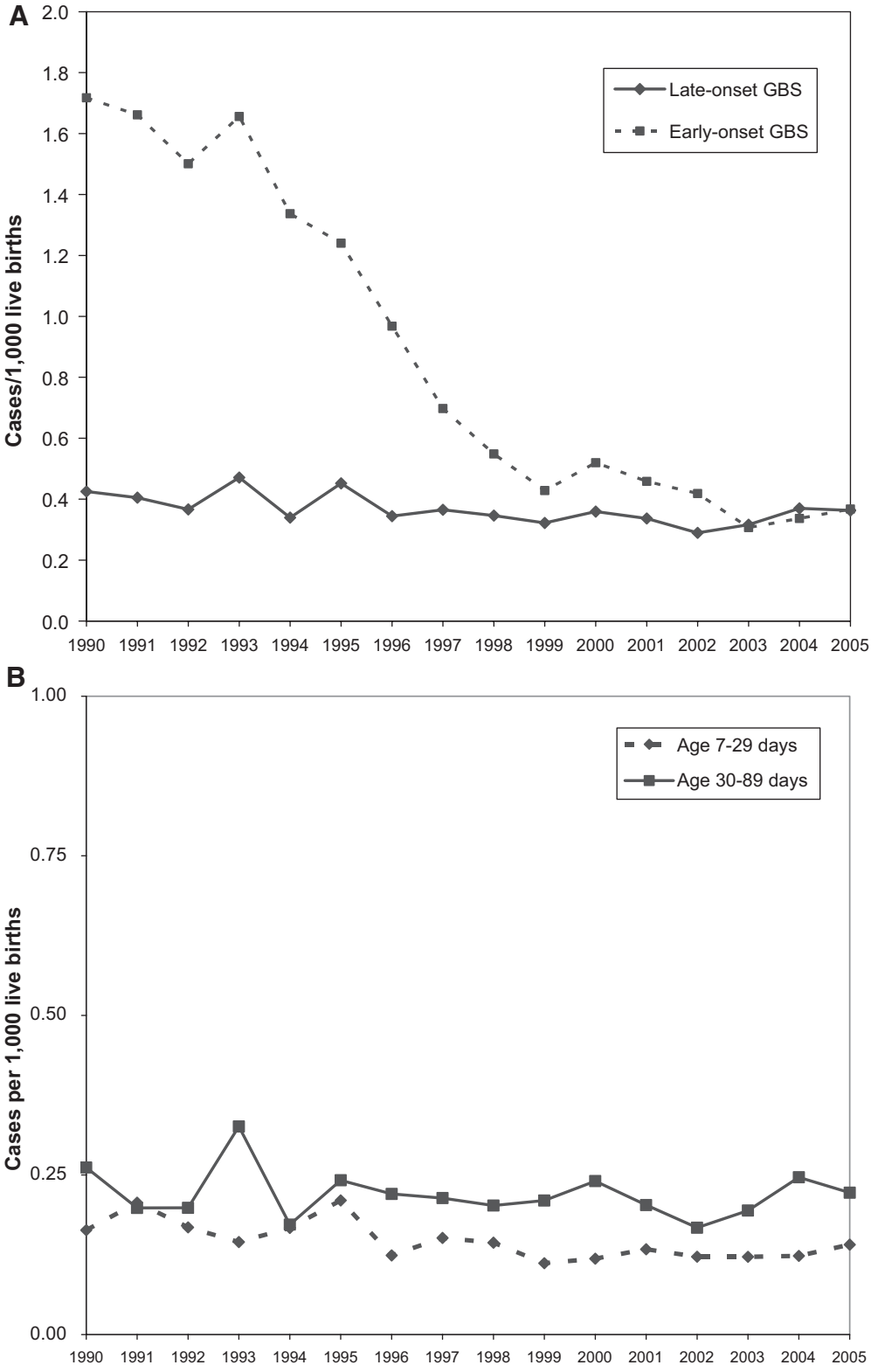

FIGURE 1. A, Incidence of early- and late-onset invasive group B streptococcal disease (GBS) in 10 U.S. surveillance areas, 1990–2005. B, Incidence of invasive group B streptococcal disease in 2 subsets of late-onset group B streptococcal disease, ages 7–29 days and 30–89 days.

TABLE 1. Incidence, Clinical Presentation, and Case-Fatality Ratio for Cases of Invasive Late-Onset Group B Streptococcal Disease in 10 U.S. Surveillance Areas Between 1990 and 2005, by Period of Prevention for Early Onset Group B Streptococcal Disease

Prevention Period, Year	Population Under Surveillance	n	Incidence/1000 Live Births	Median Onset of Illness (d)	Percent Presenting With Meningitis	Case Fatality Ratio (per 100)
Period of limited neonatal prevention						
1990	122,279	52	0.43	36	27	4.9
1991	120,979	49	0.41	29	35	17.8
1992	196,528	72	0.37	31	25	1.4
1993	193,245	91	0.47	40	29	2.2
1994	191,502	65	0.34	30	26	4.8
1995	190,289	86	0.45	31	22	1.2
Transition to widespread adoption of prevention policy						
1996	290,372	100	0.34	39	30	3.1
1997	304,040	111	0.37	37	21	1.8
1998	326,434	113	0.35	33	21	4.4
1999	366,635	118	0.32	35	25	4.3
2000	386,798	139	0.36	41	30	6.5
2001	419,062	141	0.34	35	30	5.7
2002	418,244	121	0.29	36	22	6.7
Era of universal screening						
2003	427,073	135	0.32	36	22	3.0
2004	454,505	168	0.37	39	26	4.2
2005	454,505	165	0.36	35	33	3.1

Based on surveillance data from 2003 through 2005, we estimate that 1300 cases of late-onset GBS occur in the United States annually, and that approximately 350 of these present with meningitis.

Serotype Distribution and Vaccine Formulation Implications. Seven hundred eighty-five cases of late-onset GBS disease occurred in surveillance areas that participated in isolate collection for any period between 1992 and 2005; serotyping was performed on 653 (83%) of these. Serotype was available for 157 (86%) of 182 meningitis cases which occurred in areas with isolate collection, 60% of which were due to serotype III. Compared with infection with other serotypes, infection with serotype III conferred an elevated risk of presenting with meningitis (RR: 1.3; 95% CI: 1.0–1.6).

Serotypes III, IA, and V were the most common serotypes throughout the study period, together accounting for 586 (90%) of cases with a known serotype (Table 4). The proportion of cases caused by these 3 serotypes did not differ significantly by race (blacks: 88%; nonblacks: 91%; $\chi^2 = 1.61$; $P = 0.20$).

Between 2003 and 2005, the years when gestational age data were available, 315 cases of late-onset GBS disease occurred in areas with ongoing isolate collection. Both gestational age and serotype were available for 262 (83%) of these infants. Serotypes III, IA, and V caused 227 (87%) of these cases (full-term: 92%; preterm: 82%; $\chi^2 = 5.26$; $P = 0.02$). Infection with serotype III caused a smaller proportion of preterm cases than full-term cases (39% versus 67%; $\chi^2 = 20.31$; $P < 0.001$), while serotype V was more common in preterm case-infants than full-term case infants (20% versus 5%; $\chi^2 = 13.13$; $P < 0.001$). Among the 227 cases due to serotypes III, IA, and V, gestational age was less than 34 weeks for 81 cases (36%) and 34 weeks or greater for 146 cases (64%).

Antibiotic Susceptibility. Antibiotic susceptibility testing was performed on 457 (70%) of 655 isolates from sites with isolate collection between 1996 and 2005. All isolates were susceptible to penicillin, ampicillin, and vancomycin. There are no minimum inhibitory concentration breakpoints for cefazolin; all 423 isolates tested for cefazolin sensitivity were below a minimum inhibitory concentration of 1. Twenty-seven percent of isolates were resistant to erythromycin and 12% were resistant to clindamycin.

DISCUSSION

This study provides a comprehensive, population-based depiction of trends in late-onset neonatal GBS disease between 1990 and 2005, a period of important changes in prevention strategies for early-onset GBS disease. In contrast to the marked decline in early-onset GBS disease seen during this period, there were no major shifts in the incidence of late-onset GBS disease; even among infants with disease onset on day 7–29 of life, intrapartum antibiotics do not seem to prevent the development of GBS disease.

Late-onset GBS infections cause a substantial burden of disease in the United States; the estimated number of annual cases has been similar to that for early-onset GBS disease since 2003.[22] In keeping with an earlier report from this surveillance system,[5] over one quarter of late-onset GBS cases in this study presented with meningitis, which may lead to serious disability in approximately one-third of survivors.[36] In addition to death and long-term sequelae, late-onset GBS disease often leads to lengthy hospitalizations, likely incurring considerable cost of care.[23] Prevention of late-onset GBS disease warrants renewed attention, particularly as advances in neonatal care enable preterm and low birth weight infants to survive the first week of life.

Although serotype data were available for only a small percentage of cases from the early years of this study, our results provide population-based evidence that 3 dominant

TABLE 2. Characteristics of Infants With Late-Onset Neonatal Group B Streptococcal Disease (GBS), 2003–2005

Characteristic	Percentage With Characteristic (N = 455*)
Sex (male)	52
Race	
White	43
Black	42
Other	6
Unknown	9
Ethnicity	
Hispanic	18
Non-Hispanic	55
Unknown	27
Gestational age	
≥37 wks	46
34–36 wks	13
≤33 wks	36
Unknown	5
Documented birth weight	
≥2500 g	52
1500–2499 g	15
<1500 g	29
Unknown	4
Mode of delivery	
Vaginal	52
Caesarian section	42
Unknown	6
Documented maternal prenatal GBS screening	40
Documented positive GBS screening results	46†
Exposed to intrapartum antibiotics	47
Clinical course before onset of GBS illness	
Discharged home after birth then readmitted with GBS	70
Remained hospitalized between birth and GBS illness	24
Unknown	6
Duration of hospitalization before first positive GBS culture	
<3 d	67
≥3 d	28
Unknown	5

*Enhanced data available for 455 (97%) of 468 cases occurring between 2003–2005.
†Eighty-three (46%) of 182 women with documented results had positive prenatal GBS screening.

TABLE 3. Univariate Analysis of Risk Factors Associated With Death Among 453 Infants With Known Outcome of Late-Onset Neonatal Group B Streptococcal Disease, 2003–2005

Characteristic	Died N = 15 n (%)	Survived N = 438 n (%)	Relative Risk (95% Confidence Interval)
Black race*	6 (43)	187 (47)	0.9 (0.3–2.4)
Male sex	11 (73)	224 (51)	2.6 (0.8–7.9)
Presentation with meningitis	6 (40)	118 (27)	1.8 (0.6–4.9)
Onset at 7-29 days of age	6 (40)	159 (36)	1.2 (0.4–3.2)
Preterm birth†	12 (80)	210 (50)	3.8 (1.1–13.2)
Birth weight <1500 g‡	10 (71)	121 (29)	5.8 (1.9–18.1)

*Race known for 415 cases. Referent group: nonwhite case infants.
†Gestational age known for 431 cases.
‡Birth weight known for 434 cases.

TABLE 4. Serotypes of Isolates From Cases of Invasive Late-Onset Group B Streptococcal Disease, 1992–2005*

Serotype	1992–1994 N = 78 n (%)†	1996–2002 N = 303 n (%)‡	2003–2005 N = 272 n (%)§
IA	20 (26)	76 (25)	59 (22)
IB	5 (7)	18 (6)	18 (7)
II	1 (1)	4 (1)	5 (2)
III	47 (60)	157 (52)	143 (52)
IV	0 (0)	0 (0)	9 (3)
NT	1 (1)	3 (1)	3 (1)
V	4 (5)	45 (15)	35 (13)

*Serotype available for 653 (83%) of 785 cases which occurred in surveillance areas with ongoing isolate collection.
†Serotype available for 78 (60%) of isolates from areas with isolate collection 1992–1994: Georgia and Maryland.
‡Serotype available for 303 (89%) of isolates from areas with isolate collection 1996–2002: Colorado, Georgia, Minnesota, New York, and Oregon.
§Serotype available for 272 (86%) of isolates from areas with isolate collection 2003–2005: same as 1996-2002 with addition of Maryland and New Mexico.

serotypes caused the majority of late-onset GBS cases occurring between 1992 and 2005. The relative stability in serotype distribution is encouraging for vaccine development. Assuming that placental transfer of maternal antibodies to the fetus could offer protection against GBS disease to neonates born at 34 weeks gestation or later,[37] our results indicate that administration of a maternal vaccine effective against serotypes III, IA, and V early in the third trimester of pregnancy could have prevented up to 64% of cases due to these serotypes, or 56% of all late-onset GBS cases. Serotypes IA, III, and V are responsible for the majority of early-onset and adult GBS cases as well,[38–40] so a vaccine targeting these serotypes holds promise for disease prevention across age groups.

This is a propitious time to examine the prospects for vaccine prevention of late-onset GBS disease, as the recent recommendation for use of human papilloma virus vaccine has made routine vaccination of adolescent girls a relevant, viable strategy. Vaccination during adolescence would provide ample time for the maternal immune system to form protective GBS antibodies before placental antibody transfer. It is also conceivable that vaccination before pregnancy could provide protection against maternal GBS colonization,[41] thereby decreasing transmission irrespective of gestational age. To date, this remains untested. Unfortunately, vaccination during adolescence or during the third trimester of pregnancy would likely have a limited impact among many of the preterm infants at highest risk for late-onset infections because the time window for transplacental antibody transfer is reduced for these infants. Nonetheless, our results indicate that the majority of late-onset GBS cases could have been prevented if maternal vaccination against serotypes III, IA, and V occurred in time for adequate placental antibody transfer.

This study offers reassurance that widespread intrapartum antibiotic use for early-onset GBS disease prevention has not had a negative impact on the clinical presentation or outcome of late-onset infections. In confirmation of previous reports,[42–45] all GBS isolates tested in this study were sus-

ceptible to β-lactam antibiotics, first-line choices for empiric treatment of neonatal sepsis and for intrapartum GBS antibiotic prophylaxis. We found no evidence that early-onset disease is simply delayed, rather than prevented, by intrapartum antibiotic use; if this were the case, the incidence of late-onset GBS disease, particularly within the 7–29 day age group, would have risen rather than remained stable, and the median age of onset of late-onset disease would have shifted earlier into the 7–89 day period, rather than later, as observed.

Black race (42%), prematurity (49%), and maternal prenatal GBS colonization (49%) were common among infants with late-onset GBS disease; in comparison, a survey of births occurring in ABCs surveillance sites between 1998 and 1999 found that 15% of the general birth cohort was black, 11% was born prematurely, and 24% of mothers had prenatal GBS colonization.[11] The overrepresentation of these characteristics among late-onset disease cases is consistent with risk factors identified previously.[12,13] As is true for early-onset disease,[8] the incidence of late-onset GBS disease is at least 3 times higher among black infants than among white infants, which may be related to higher rates of GBS colonization[46,47] or preterm birth[30]among black women, or to disparities in access to prenatal care.[48] Incidence in black infants remained at least triple that in nonblack infants when our data were stratified by gestational age, suggesting that differential rates of prematurity do not explain the disparity. Whether the rise in disease incidence among black infants between 2002 and 2005 reflects a sustained trend is an important question requiring attention through continued surveillance.

Over one-quarter of case-infants in this study were hospitalized for at least 3 days before the first positive GBS culture was obtained. These infections could have resulted from surface colonization acquired during labor and delivery, or may have been transmitted to the infants by hospital staff or visiting family. Regardless, these results suggest that infection control could play a role in a preventing a substantial proportion of late-onset GBS cases. Further exploration of how transmission occurred in the non-nosocomial cases could provide important information on factors contributing to GBS acquisition within the home.

Although the large number of late-onset GBS cases provided substantial statistical power, our study is limited by the scope of the chart review performed for each case. Information on the management of GBS disease is not collected, thereby preventing assessment of the role of treatment decisions in clinical outcomes. Also, important data such as gestational age and birth weight were not complete for cases occurring before 2003, preventing examination of whether these factors influenced trends in late-onset GBS disease. Small numbers limited our ability to perform a detailed analysis of risk factors for death, and the lack of a healthy comparison group prevented exploration of risk factors for disease. Additionally, our projections about potential vaccine preventability of late-onset GBS disease relied on simplified assumptions of antibody dynamics, placental antibody transfer, and vaccine effectiveness.

Late-onset GBS disease prevention will likely require a multipronged strategy, including vaccination. Although a better understanding of risk factors for and transmission of late-onset GBS disease could help accelerate prevention efforts, opposition to testing and use of vaccines in pregnant women presents a major hurtle.[24] Confronting these concerns is crucial to the prevention not only of late-onset GBS disease but of neonatal GBS disease in general.

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