Epidemiology of Invasive Early-Onset and Late-Onset Group B Streptococcal Disease in the United States, 2006 to 2015
Multistate Laboratory and Population-Based Surveillance

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IMPORTANCE Invasive disease owing to group B *Streptococcus* (GBS) remains an important cause of illness and death among infants younger than 90 days in the United States, despite declines in early-onset disease (EOD; with onset at 0-6 days of life) that are attributed to intrapartum antibiotic prophylaxis (IAP). Maternal vaccines to prevent infant GBS disease are currently under development.

OBJECTIVE To describe incidence rates, case characteristics, antimicrobial resistance, and serotype distribution of EOD and late-onset disease (LOD; with onset at 7-89 days of life) in the United States from 2006 to 2015 to inform IAP guidelines and vaccine development.

DESIGN, SETTING, AND PARTICIPANTS This study used active population-based and laboratory-based surveillance for invasive GBS disease conducted through Active Bacterial Core surveillance in selected counties of 10 states across the United States. Residents of Active Bacterial Core surveillance areas who were younger than 90 days and had invasive GBS disease in 2006 to 2015 were included. Data were analyzed from December 2017 to April 2018.

EXPOSURES Group B *Streptococcus* isolated from a normally sterile site.

MAIN OUTCOMES AND MEASURES Early-onset disease and LOD incidence rates and associated GBS serotypes and antimicrobial resistance.

RESULTS The Active Bacterial Core surveillance program identified 1277 cases of EOD and 1387 cases of LOD. From 2006 to 2015, EOD incidence declined significantly from 0.37 to 0.23 per 1000 live births ($P < .001$), and LOD rates remained stable (mean, 0.31 per 1000 live births). Among the mothers of 1277 infants with EOD, 617 (48.3%) had no indications for IAP and did not receive it, and 278 (21.8%) failed to receive IAP despite having indications. Serotype data were available for 1743 of 1897 patients (91.3%) from 7 sites that collect GBS isolates. Among patients with EOD, serotypes Ia (242 [27.3%]) and III (242 [27.3%]) were most common. Among patients with LOD, serotype III was most common (481 [56.2%]), and this increased from 2006 to 2015 from 0.12 to 0.20 cases per 1000 live births ($P < .001$). Serotype IV caused 53 cases (6.2%) of EOD and LOD combined. The 6 most common serotypes (Ia, Ib, II, III, IV, and V) caused 881 EOD cases (99.3%) and 853 LOD cases (99.7%). No β-lactam resistance was identified; 359 isolates (20.8%) tested showed constitutive clindamycin resistance. In 2015, an estimated 840 EOD cases and 1265 LOD cases occurred nationally.

CONCLUSIONS AND RELEVANCE The rates of LOD among US infants are now higher than EOD rates. Combined with addressing IAP implementation gaps, an effective vaccine covering the most common serotypes might further reduce EOD rates and help prevent LOD, for which there is no current public health intervention.

Supplemental content

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Group B *Streptococcus* (GBS) remains a leading infectious cause of morbidity and mortality among infants in the United States[1] despite marked declines in disease during the first week of life (early-onset disease [EOD]) through widespread implementation of guidelines for intrapartum antibiotic prophylaxis (IAP).[2-6] Of the EOD cases that occur in the United States annually, a portion may be preventable by improved implementation of existing IAP guidelines.[7] However, GBS disease among infants aged 7 to 89 days (late-onset disease [LOD]) is not prevented by IAP.[8] Moreover, more than 30% of infants delivered in the United States are now exposed to intrapartum antibiotics, raising concern about potential for emergence of antibiotic resistance in GBS or other neonatal pathogens, as well as unintended consequences from disruption of the establishment of the newborn microbiota.[9-12] Maternal immunization represents a nonantibiotic strategy to prevent both EOD and LOD. Multivalent polysaccharide-protein conjugate vaccines are under development against GBS capsular types, with candidate vaccines in phase I and II trials.[13,14]

To guide refinement of current perinatal GBS disease prevention approaches and vaccine development, we analyzed data from a multistate surveillance system capturing approximately 10% of US live births to describe EOD and LOD epidemiology, incidence trends, and associated GBS strain characteristics. We also describe potential gaps in implementation of existing IAP guidelines among EOD cases.

Methods

Surveillance

Active Bacterial Core surveillance (ABCs) conducts active, population-based and laboratory-based surveillance for invasive GBS disease among infants in select counties of 10 states across the United States.[15,16] In 2015, it included an area with 439 151 live births. From 2006 to 2015, GBS surveillance was consistent in San Francisco, California (3 counties); Denver, Colorado (5 counties); Atlanta, Georgia (20 counties); Portland, Oregon (3 counties); Rochester and Albany, New York (15 counties); multiple urban areas in Tennessee (11 counties); and the entire states of Connecticut, Maryland, Minnesota, and New Mexico. The staff of ABCs contacted laboratories serving surveillance area residents for ascertainment of GBS culture–positive cases. Standardized case report forms capturing clinical data, epidemiological data, and intrapartum history, including administration of recommended IAP antibiotics (penicillin, ampicillin, cefazolin, clindamycin, or vancomycin), were completed through review of medical and maternal labor and delivery records. The methods of ABCs, including those used for the identification of clinical syndromes, determination of race, and ascertainment of death as a hospitalization outcome are detailed elsewhere.[5,17]

Ethical Considerations

The ABCs case reporting and isolate collection were reviewed in accordance with Centers for Disease Control and Prevention human research protection procedures and were determined to be nonresearch public health surveillance. The ABCs sites reviewed the protocol and obtained institutional review board approval where required.

Definitions

An invasive case was defined as isolation of GBS from a normally sterile site from a surveillance area resident. Infants born at 37 or more completed weeks' gestation were categorized as being born full term.

Considerations for Vaccine Protection
Based on Gestational Age and Age at Disease Onset

Transplacental transfer of maternal antibodies peaks after 32 to 33 weeks' gestation, and transferred antibodies then steadily decline after birth as the infant ages.[18] Efficacy of a maternal vaccine might therefore be lower in preventing GBS disease in infants born preterm, particularly before peak antibody transfer, and/or infants with disease onset more than 42 days after birth (which is the half-life of anti-GBS IgG in infants[19]).[18,20] Therefore, for this analysis, we compared characteristics of cases in infants born at less than 35 weeks' gestation or with disease onset after 42 days of life with those born at 35 or more weeks' gestation or with disease onset within the first 42 days of life.

Specimen Collection and Testing

During the study period, 7 sites (in Colorado, Georgia, Maryland, Minnesota, New Mexico, New York, and Oregon) collected isolates. All serotyping and antimicrobial susceptibility testing were done at the US Centers for Disease Control and Prevention *Streptococcus* laboratory, except for susceptibility testing for isolates from Minnesota, which were tested at the Minnesota Department of Public Health. Isolates were serotyped by latex agglutination test using rabbit antisera to capsular polysaccharide types Ia, Ib, and II through IX.[21] Beginning in 2007, polymerase chain reaction serotyping was performed on isolates that were nontypeable by latex agglutination. Antimicrobial susceptibility testing was by broth dilution methods, and minimum inhibitory concentrations were interpreted according to the Clinical and Laboratory Standards Institute guidelines.[22] Constitutive resistance to clindamycin was determined by the broth dilution method. Begin-

Table. Characteristics of Patients With Early-Onset Disease and Late-Onset Disease, 2006 to 2015

Characteristic	Patients, No. (%)	
	Early-Onset Disease	Late-Onset Disease
Total	1277	1387
Gestational age		
Term	919 (72)	727 (52.4)
Preterm	351 (27.5)	580 (41.8)
Unknown	7 (0.6)	80 (5.8)
Died, No./total No. (%)	88/1277 (6.9)	75/1387 (5.4)
Term	19/919 (2.1)	25/727 (3.4)
Preterm	67/351 (19.1)	45/580 (7.8)
Unknown	2/7 (28.6)	5/80 (6.3)
Female	607 (47.5)	702 (50.6)
Race/ethnicity		
White	705 (55.2)	706 (50.9)
Black	498 (39.0)	588 (42.4)
Other	74 (5.8)	94 (6.8)
Source of isolate[a]		
Blood	1266 (99.1)	1284 (92.6)
Cerebrospinal fluid	48 (3.8)	287 (20.7)
Joint fluid	0	16 (1.2)
Bone	0	5 (0.4)
Peritoneal fluid	0	3 (0.2)
Syndrome[b]		
Bacteremia without focus	1061 (83.1)	847 (61.1)
Meningitis	121 (9.5)	435 (31.4)
Bacteremic pneumonia	76 (6)	26 (1.9)
Septic shock	13 (1)	39 (2.8)
Arthritis	1 (0.1)	21 (1.5)
Peritonitis	0	4 (0.3)

[a] Total of proportions could be more than 100% because some cases had isolates from more than 1 source.

[b] Total of proportions could be more than 100% because some cases had more than 1 syndrome identified; no other syndrome overlapped with bacteremia without focus.

ning in 2011, macrolide-inducible clindamycin resistance was determined using the erythromycin-clindamycin combination–well broth dilution method.[23,24] For isolates from 2015, whole-genome sequencing data were available and analyzed using a validated bioinformatics pipeline for assessment of antimicrobial resistance phenotypes, multilocus sequence typing (https://pubmlst.org/sagalactiae/), and capsular serotypes.[25]

Statistical Analysis

We calculated incidence rates using ABCs case counts as the numerator and the number of live births as the denominator. We used state vital records and national vital statistics reports to obtain ABCs site–specific live birth data. Linear trends in incidence rates were evaluated using the Cochran-Armitage test. For incidence rates that had a statistically significant departure from linearity, trends were assessed using the nonparametric Mann-Kendall test. A P value less than .05

was considered statistically significant, and χ^2 tests were used to compare distributions of categorical variables. Data were analyzed using SAS version 9.4 (SAS Institute Inc). National estimates of cases were obtained by applying the age and racial distribution of the US population in 2015 to the race-and-age-specific rates obtained from the ABCs surveillance areas. Data were analyzed from December 2017 to April 2018.

Results

Description of GBS Cases

We identified 1277 cases of EOD from 2006 to 2015 across the surveillance areas (Table). In the same period and geographical areas, we identified 1387 cases of LOD. Recurrent cases in the same individual were not recorded, and thus an exact number of affected infants was not determined.

Most EOD cases (1209 [94.7%]) occurred within 48 hours of birth, and 351 (27.5%) were in preterm infants. In all EOD cases, an isolate was collected either from blood (1266 [99.1%]) and/or cerebrospinal fluid (CSF) (48 [3.8%]). Cerebrospinal fluid was the only isolate source in 11 cases (0.1%) in 8 full-term and 3 preterm infants. Of 121 cases of EOD meningitis, 31 (25.6%) were in preterm infants. The overall EOD case-fatality rate was 6.9% (88 of 1277; in full-term infants, 19 of 919 [2.1%]; in preterm infants, 67 of 351 [19.2%]; in infants of unknown gestational age, 2 of 7 [28.6%]). We identified 14 cases in which patients had documented discharges from the birth hospital before readmission with EOD.
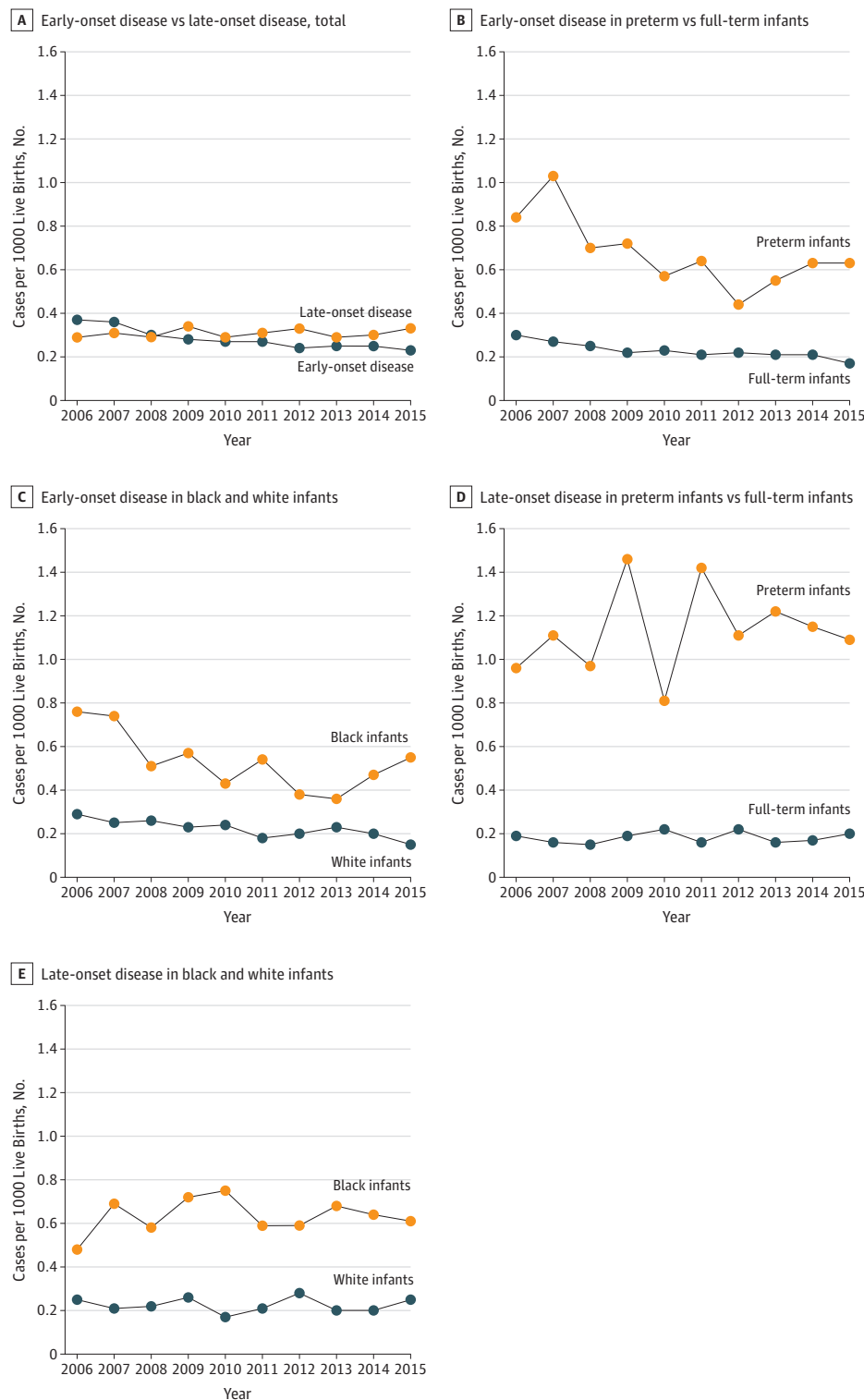
The median (interquartile range [IQR]) patient age at positive culture for LOD was 34 (20-49) days, and 580 cases (41.8%) were in preterm infants. Most patients with LOD had isolates from blood (1284 [92.6%]) and/or CSF (287 [20.7%]) (Table); CSF was the only isolate source from 84 patients (6.1%). Of 435 LOD meningitis cases, 158 (36.3%) were in preterm infants. The overall LOD case-fatality rate was 75 of 1387 (5.4%; full-term infants, 25 of 727 [3.4%]; preterm infants, 45 of 580 [7.8%]; in infants of unknown gestational age, 5 of 80 [6.3%]). The case-fatality rate for LOD cases identified as meningitis (42 of 435 [9.7%]) was higher than that of cases that were not identified as meningitis (33 of 952 [3.5%]; $P < .001$).

For 2015, we estimated a projected national burden of 840 EOD cases. Additionally, a national burden of 1265 LOD cases was estimated.

Trends in EOD

From 2006 to 2015, EOD incidence declined overall (from 0.37 to 0.23 per 1000 live births; $P < .001$; **Figure 1**) and when stratified by gestational age (in full-term infants, from 0.30 to 0.17 per 1000 live births; $P < .001$; in preterm infants, from 0.84 to 0.63 per 1000 live births; $P = .002$; Figure 1). From 2006 to 2015, annual EOD rates were higher among preterm infants than full-term infants (mean [range] rate ratio, 3.0 [2.0-3.8] times) and black infants compared with white infants (mean [range] rate ratio, 2.4 [1.6-3.7] times). There was a statistically significant decline in EOD among white infants (from 0.29 to 0.15 per 1000 live births; $P < .001$) and black infants (from 0.76 to 0.55 per 1000 live births; $P = .04$).

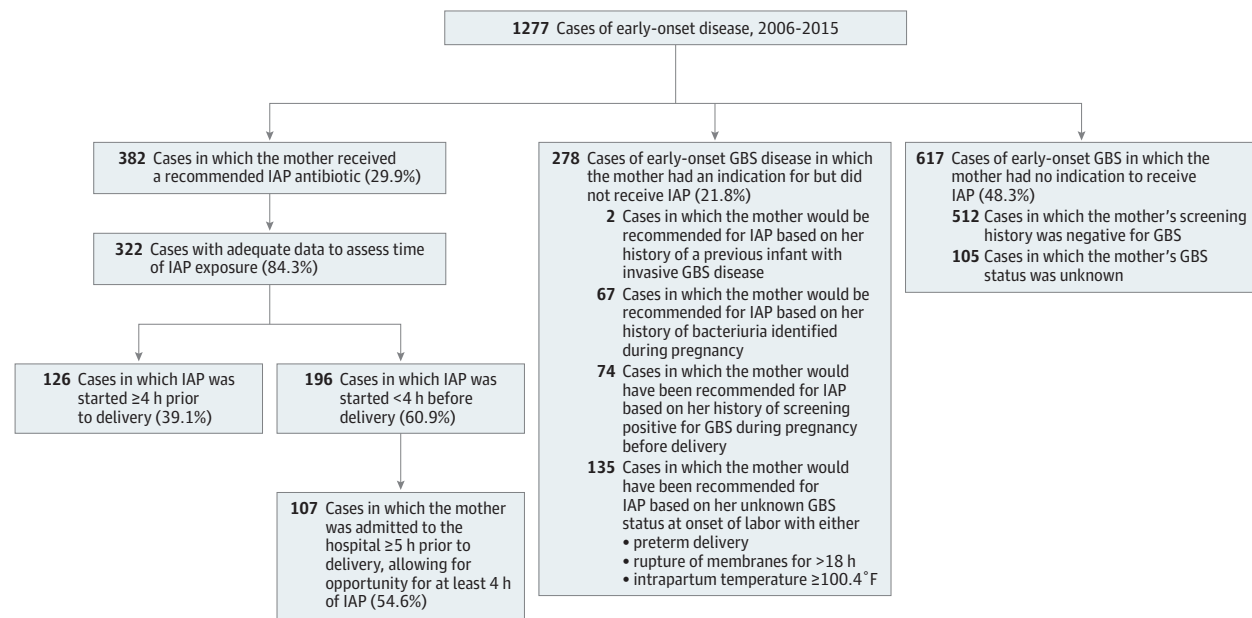Figure 1. Rates of Early-Onset and Late-Onset Invasive Group B Streptococcal Disease

A Early-onset disease vs late-onset disease, total

B Early-onset disease in preterm vs full-term infants

C Early-onset disease in black and white infants

D Late-onset disease in preterm infants vs full-term infants

E Late-onset disease in black and white infants

Missed Opportunities for Prevention of EOD Under Current IAP-Based Prevention Guidelines

Overall, 617 mothers of 1277 infants with EOD (48.3%) had no indication for and did not receive IAP, and 278 of 1277 mothers (21.8%) failed to receive IAP despite an indication of need

(Figure 2). Among the mothers of infants with EOD who received a recommended IAP antibiotic, an incorrect agent was common among those with penicillin allergy but no history of associated anaphylaxis, angioedema, respiratory distress, or urticaria; 55 of 57 (96%) received clindamycin instead of

Figure 2. Description of Missed Opportunities for Intrapartum Antibiotic Prophylaxis (IAP) Among Early-Onset Disease Cases, 2006 to 2015

1277 Cases of early-onset disease, 2006-2015

382 Cases in which the mother received a recommended IAP antibiotic (29.9%)

322 Cases with adequate data to assess time of IAP exposure (84.3%)

126 Cases in which IAP was started ≥4 h prior to delivery (39.1%)

196 Cases in which IAP was started <4 h before delivery (60.9%)

107 Cases in which the mother was admitted to the hospital ≥5 h prior to delivery, allowing for opportunity for at least 4 h of IAP (54.6%)

278 Cases of early-onset GBS disease in which the mother had an indication for but did not receive IAP (21.8%)
  2 Cases in which the mother would be recommended for IAP based on her history of a previous infant with invasive GBS disease
  67 Cases in which the mother would be recommended for IAP based on her history of bacteriuria identified during pregnancy
  74 Cases in which the mother would have been recommended for IAP based on her history of screening positive for GBS during pregnancy before delivery
  135 Cases in which the mother would have been recommended for IAP based on her unknown GBS status at onset of labor with either
    • preterm delivery
    • rupture of membranes for >18 h
    • intrapartum temperature ≥100.4˚F

617 Cases of early-onset GBS in which the mother had no indication to receive IAP (48.3%)
  512 Cases in which the mother's screening history was negative for GBS
  105 Cases in which the mother's GBS status was unknown

GBS indicates group B streptococcal disease.

cefazolin.[4] Among 322 cases of EOD with adequate data to evaluate duration of antibiotic exposure, 196 mothers (60.9%) had received IAP for less than 4 hours before delivery; of these, 107 cases of EOD were in newborns whose mothers were admitted to the hospital 5 or more hours before delivery and would have had an opportunity to receive IAP for an adequate duration.

Among mothers of infants with EOD who did not receive IAP and had no indication of need, 512 of 617 (83.0%) had negative GBS screening test results; among those who did not receive IAP and had an indication of need, unknown GBS status and presence of a clinical risk factor was the most common scenario (135 of 278 mothers [48.6%]). Thirteen cases of EOD occurred among infants whose mothers had no indication for IAP and underwent cesarean delivery before onset of labor and rupture of membranes.

Trends in LOD

The incidence of LOD remained stable overall (mean, 0.31 per 1000 live births) and when stratified by gestational age at delivery or race (Figure 1). From 2006 to 2015, annual LOD rates were higher among preterm infants compared with term infants (mean [range] rate ratio, 6.4 [3.7-7.7] times) and black infants compared with white infants (mean [range] rate ratio, 2.9 [1.9-4.4] times).

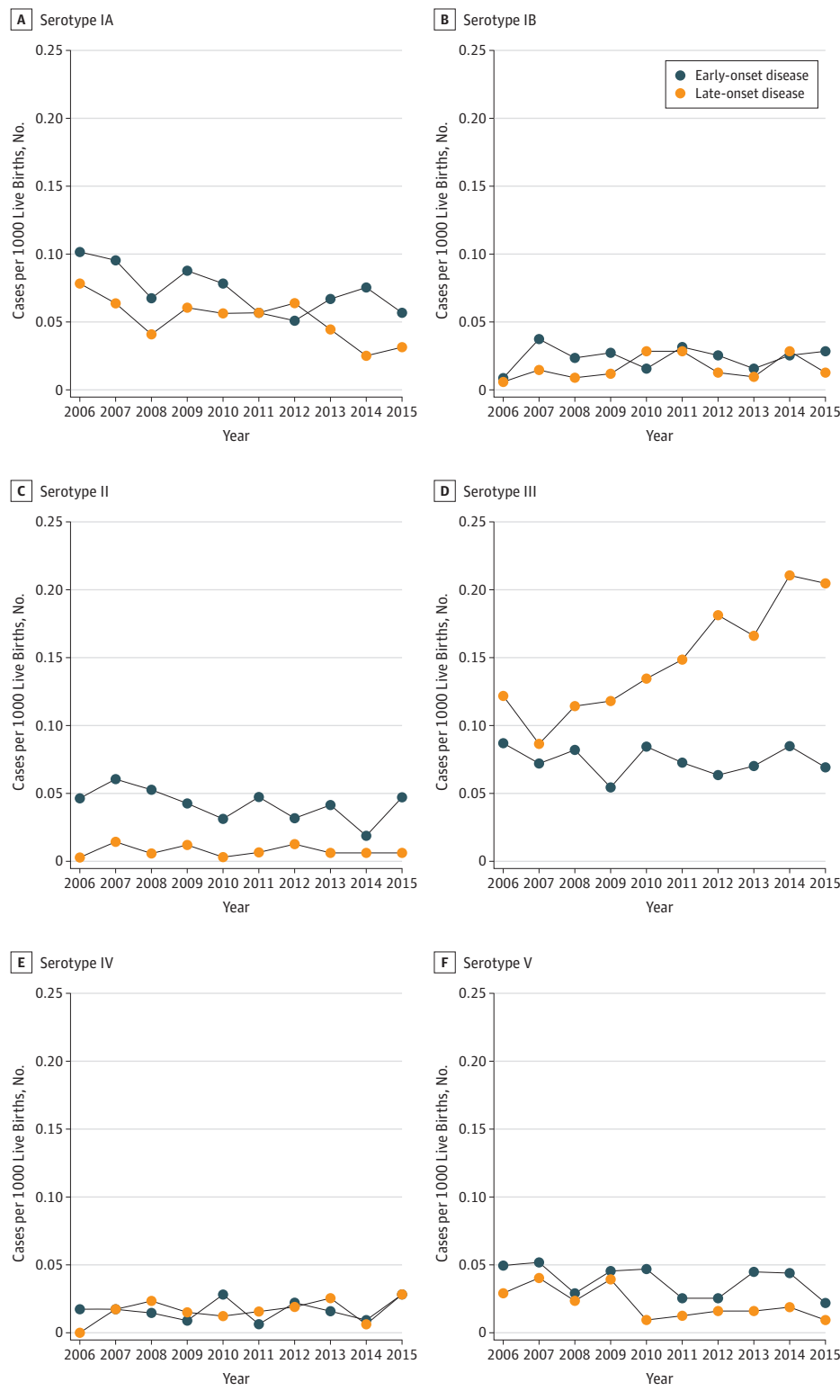### Serotypes and Antimicrobial Susceptibility

Among sites that collected isolates, serotype data were available for 887 of 959 cases of EOD (92.5%) and 856 of 938 cases of LOD (91.3%). Antimicrobial susceptibility data were available for 877 of 959 cases of EOD (91.5%) and 850 of 938 cases of LOD (90.6%).

The incidence of EOD owing to serotype Ia declined significantly (from 0.10 per 1000 live births in 2006 to 0.06 per 1000 live births in 2015; *P* = .01) while that of EOD owing to other serotypes did not show any significant change (**Figure 3**). Overall, of 887 EOD cases with serotype data, 826 (93.1%) were caused by serotypes Ia (242 [27.3%]), III (242 [27.3%]), II (138 [15.6%]), V (126 [14.2%]), and Ib (78 [8.8%]), which are components of proposed multivalent vaccines. The proportion of EOD cases owing to serotype IV ranged over the study years from 3.4% (3 of 89 cases in 2009) to 11.3% (9 of 80 in 2015), with no significant trend per the Cochran-Armitage trend test. Together, serotype IV and these 5 other most frequent serotypes caused 881 EOD cases (99.3%).

From 2006 to 2015, LOD incidence owing to serotype III increased significantly (from 0.12 to 0.20 per 1000 live births; *P* < .001) and that of EOD owing to serotype Ia (0.08 to 0.03 per 1000 live births; *P* = .004) and serotype V (0.03 to 0.01 per 1000 live births; *P* = .003) declined (Figure 3). Among 856 cases of LOD with serotype data, the 5 most frequent serotypes were III (481 [56.2%]), Ia (171 [20.0%]), V (71 [8.3%]), IV (53 [6.2%]), and Ib (52 [6.1%]). In combination, serotype II and these 5 serotypes caused 853 LOD cases (99.7%). The proportion of LOD owing to serotype IV ranged over the study years from 0% (0 of 82 cases in 2006) to 10.7% (8 of 75 cases in 2008), with no significant trend per the Cochran-Armitage trend test.

All 1727 isolates tested were susceptible to penicillin, ampicillin, and vancomycin; 774 (44.8%) had erythromycin resistance, and 359 (20.8%) had constitutive clindamycin resistance (**Figure 4**). From 2006 to 2015, the proportion of erythromycin resistance increased significantly (66 of 190 [34.7%] in 2006 to 85 of 173 [49.1%] in 2015; *P* = .02); no significant trend was seen for proportion of constitutive clinda-

Figure 3. Incidence of Early-Onset and Late-Onset Group B Streptococcal Disease by Serotype, 2006 to 2015
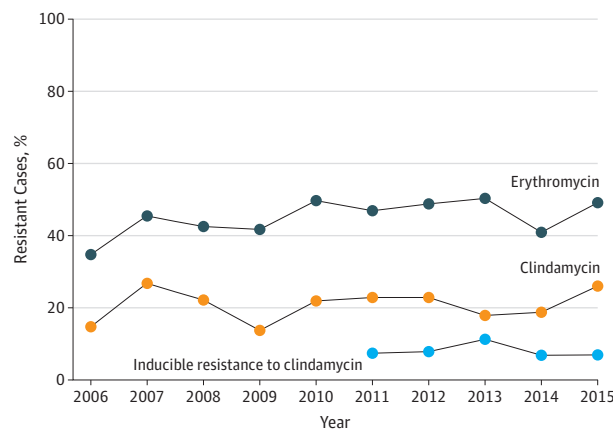

Of the 10 Active Bacterial Core surveillance sites, only those in Colorado, Georgia, Maryland, Minnesota, New Mexico, New York, and Oregon collect isolates for characterization including serotyping and antimicrobial susceptibility testing.

mycin resistance (28 of 190 [14.7%] in 2006 to 45 of 173 [26.0%]; P = .32). The proportion of isolates with resistance was highest for serotype II (erythromycin resistance, 107 of 161 [66.5%]; constitutive clindamycin resistance, 87 of 161 [54.0%]) and serotype V (erythromycin resistance, 118 of 193 [61.1%]; constitutive clindamycin resistance, 93 of 193 [48.2%]). Of 750 isolates tested since 2011 for macrolide-inducible clindamycin resistance, 70 (9.3%) were positive.

Figure 4. Trends in Percentage of Macrolide Resistance Among Isolates Collected and Tested Through Active Bacterial Core Surveillance Sites, 2006 to 2015

Data on macrolide-inducible clindamycin resistance were available only from 2011 onward. Of the 10 Active Bacterial Core surveillance sites, only those in Colorado, Georgia, Maryland, Minnesota, New Mexico, New York, and Oregon collect isolates for characterization including serotyping and antimicrobial susceptibility testing.

In 2015, 173 of the 185 isolates (93.5%) available were sequenced. Erythromycin resistance occurred in 86 isolates, and common determinants included *ermB* (28 [32.6%]), *mef* (26 [30.2%]), *ermTR* (23 [26.7%]), and *ermT* (10 [11.6%]); in 65 isolates, clindamycin resistance was associated with *ermB* (28 [43.1%]), *ermTR* (23 [35.4%]), and *ermT* (10 [15.4%]). No isolate had a penicillin-binding protein 2x (PBP2x) type associated with reduced susceptibility to β-lactams.[25] The 3 most common multilocus sequence types were ST23 (16 [20.0%]), ST22 (11 [13.8%]). and ST17 (9 [11.3%]) among 80 isolates from EOD cases and ST17 (49 [52.7%]), ST23 (7 [7.5%]), and ST19 (5 [5.4%]) among 93 isolates from LOD cases. The virulence gene *HvgA* (Hypervirulent GBS adhesin), which is associated with meningeal tropism in neonates, was present in 68 of 173 isolates (39.3%).[26] All 68 were of serotype III (constituting 68 of 87 [78.2%] of all serotype III isolates) and belonged to ST17 or its single-locus variants.

Considerations for Vaccine Protection
Based on Gestational Age and Age at Disease Onset
Among 1277 cases of EOD, 261 (20.4%) occurred in infants born at less than 35 weeks' gestational age. Among 1387 cases of LOD, 688 (49.6%) were in infants born either at less than 35 weeks' gestational age and/or those who had disease onset after 42 days of life (eFigure and eTable 1 in the Supplement). The proportion of serotypes II and V were significantly higher and serotype III significantly lower among infants with EOD born at less than 35 weeks' gestation (serotype: II, 38 of 190 [20.0%]; V, 37 of 190 [19.5%]; III, 31 of 190 [16.3%]) than those who were born at 35 weeks' gestation or more (serotype: II, 99 of 764 [13.0%]; *P* = .01; V, 88 of 764 [11.5%]; *P* = .003; serotype III, 211 of 764 [27.5%]; *P* < .001; eTable 2 in the Supplement). The proportion of serotypes Ia, IV, and V were significantly higher and serotype III significantly lower among infants with LOD who

were born either at less than 35 weeks' gestation and/or had disease onset after 42 days of life (serotypes: Ia, 97 of 458 [21.2%]; IV, 35 of 458 [7.36%]; V, 46 of 458 [10.0%]; III, 193 of 458 [42.1%]) than infants with neither trait (serotypes: Ia, 65 of 424 [15.3%]; *P* = .02; IV, 15 of 424 [3.5%]; *P* = .008; V, 20 of 424 [4.7%]; *P* = .003; III, 258 of 424 [60.9%]; *P* < .001; eTable 3 in the Supplement).

Discussion

Occurrence of GBS disease among infants remains an important problem, with an estimated 850 EOD and 1250 LOD cases nationally in 2015. Missed opportunities for prevention among EOD cases were similar to those observed in 2008[7] and shortly after the 2002 transition to universal screening.[27] Beginning in 2008, the annual rate of LOD has been higher than that of EOD. A vaccine containing the 6 leading serotypes would have covered greater than 99% of invasive disease cases in infants younger than 3 months during the study period.

While no isolates with nonsusceptibility to β-lactams were identified among GBS cases in infants younger than 3 months from 2006 to 2015, characterization of GBS isolates from cases of EOD and LOD from 2016 and the first months of 2017 has uncovered 4 isolates with β-lactam nonsusceptibility and associated substitutions within the transpeptidase domain of *PBP2x*.[28] First reported in the United States in 2003 in isolates from invasive adult disease, β-lactam nonsusceptibility continues to persist in low but slightly increasing percentages, raising the possibility of increasing prevalence in the future.[25,29] For large-scale strain surveillance, whole-genome sequencing is more sensitive than phenotypic methods at detecting single-step mutations within streptococcal *PBP2x* genes that often confer only modest decreases in β-lactam susceptibility.[25] Population-based monitoring remains crucial, because β-lactams and cephalosporins are the central agents for treatment of invasive and noninvasive GBS disease and prevention of EOD.

In 2006, EOD rates were already at a historic low (from 1.37 in the early 1990s to 0.37 per 1000 live births in 2005).[5] Rates continued to decline modestly from 2006 to 2015. Updated prevention guidelines in 2010[1,4] included minor refinements to guidance on laboratory processing of antenatal screening specimens and management of women and newborns with specific presentations. While this updated document may have contributed to the observed decrease, guideline adherence was already high in 2003 to 2004,[27] and missed opportunities for prevention among cases were similar to those preceding the issuance of the 2010 guidelines. Factors not associated with IAP implementation may also have contributed to declining EOD incidence, as was observed for the period from 1990 to 2012.[30] While the current culture-based screening strategy has been highly successful in reducing EOD burden, our data show that almost half of remaining infants with EOD were born to mothers with no indication for receiving IAP. Clinical decision support tools and other innovative methods may help reduce implementation errors, such as the use of cefazolin in women allergic to penicillin at low risk of anaphylaxis, in-

stead of clindamycin, a less effective agent with increasing rates of nonsusceptibility.[31] We identified extremely few cases occurring in infants born to mothers who underwent cesarean delivery before onset of labor and rupture of membranes, which supports the current recommendation of not requiring IAP administration to such mothers.[4] Cerebrospinal fluid was the sole source for GBS isolation in 11 infants with EOD; current guidelines recommend lumbar puncture for newborns with signs of sepsis if the infant is stable enough to tolerate the procedure.[4] While revisions to existing guidelines may further clarify and address persistent areas of challenge, an alternative strategy, such as prevention through vaccines, will likely be necessary for further significant declines in disease rates.

Although overall LOD rates were stable over the study period, serotype-specific incidence varied more in LOD than EOD, with a notable increase in LOD owing to serotype III; 2015 whole-genome sequencing data showed that 78.2% of these isolates possessed the *HvgA* gene, which is found mostly in the globally dominant multilocus sequence type ST17.[32-34] Both England and the Netherlands have reported recent increases in LOD[32,35]; in the Netherlands, this increase was associated with expansion of a particular subclade of ST17, and it will be important to monitor for this expansion elsewhere.[36]

Overall, more than 99% of disease was owing to 6 leading serotypes, suggesting that a hexavalent vaccine against these serotypes will cover almost all cases. A recent decision-analysis model of potential GBS prevention strategies in the United States[30] identified maternal immunization in conjunction with IAP, as indicated by current guidelines for unvaccinated women, as a strategy that could prevent more disease than universal screening and IAP do for a similar cost per quality-adjusted life-year. Recommendations for influenza and tetanus, diphtheria, and acellular pertussis vaccines during pregnancy have helped improve acceptability and implementation capacity for vaccination during pregnancy, and survey data suggest support among US obstetricians for a safe and efficacious maternal GBS vaccine.[37-39] However, 20.4% of EOD and 49.6% of LOD cases were among infants who were born at less than 35 weeks' gestational age and/or experienced disease onset at more than 42 days of life, and maternal vaccination might be less effective at preventing these cases. To help prevent GBS cases among preterm infants and LOD with onset beyond 42 days of life, strategies that include requirement for higher vaccine immunogenicity for serotypes Ia, II, IV, and V, which were overrepresented among these cases, may be needed.

Limitations

While ABCs is a stable surveillance system that captures invasive GBS cases from over 400 000 live births annually, it represents only 10% of US live births and may not reflect the full variation within the country. Additionally, we had only 1 year of whole-genome sequencing data and were unable to correlate disease patterns over time with changes in strain characteristics at the genomic level. Information on missed opportunities for prevention of EOD was limited to data available in the labor and delivery record and was only available for cases with no comparison group; population-level data are needed to characterize GBS prevention guideline implementation practices.

Conclusions

Despite significant declines in EOD rates attributed to IAP, the burden of EOD and LOD in the United States remains substantial. Refinements to existing IAP guidelines could improve guideline adherence and sustain current low rates of EOD. Continued microbiological surveillance for emergence of β-lactam nonsusceptibility, increasing clindamycin resistance and expansion of virulent clones such as serotype III ST17 strains, remain critical for early identification of emerging threats to the effectiveness of treatment and prevention strategies. With LOD rates higher than EOD rates, greater than half of all infant GBS disease in the United States currently is not preventable by any currently available strategy. A safe and efficacious maternal vaccine against the most common serotypes holds promise to prevent a substantial portion of this remaining burden. With candidate vaccines in advanced stages of development, surveillance to monitor disease trends and characteristics provides a key evidence base for vaccine and public health policy decisions.

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