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Epidemiology of Invasive Group B Streptococcal Infections Among Nonpregnant Adults in the United States, 2008-2016

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IMPORTANCE Group B *Streptococcus* (GBS) is an important cause of invasive bacterial disease. Previous studies have shown a substantial and increasing burden of GBS infections among nonpregnant adults, particularly older adults and those with underlying medical conditions.

OBJECTIVE To update trends of invasive GBS disease among US adults using population-based surveillance data.

DESIGN, SETTING, AND PARTICIPANTS In this population-based surveillance study, a case was defined as isolation of GBS from a sterile site between January 1, 2008, and December 31, 2016. Demographic and clinical data were abstracted from medical records. Rates were calculated using US Census data. Antimicrobial susceptibility testing and serotyping were performed on a subset of isolates. Case patients were residents of 1 of 10 catchment areas of the Active Bacterial Core surveillance (ABCs) network, representing approximately 11.5% of the US adult population. Patients were included in the study if they were nonpregnant, were 18 years or older, were residents of an ABCs catchment site, and had a positive GBS culture from a normally sterile body site.

MAIN OUTCOMES AND MEASURES Trends in GBS cases overall and by demographic characteristics (sex, age, and race), underlying clinical conditions of patients, and isolate characteristics are described.

RESULTS The ABCs network detected 21 250 patients with invasive GBS among nonpregnant adults from 2008 through 2016. The GBS incidence in this population increased from 8.1 cases per 100 000 population in 2008 to 10.9 in 2016 (P = .002 for trend). There were 3146 cases reported in 2016 (59% male; median age, 64 years; age range, 18-103 years). The GBS incidence was higher among men than women and among blacks than whites and increased with age. Projected to the US population, an estimated 27 729 cases of invasive disease and 1541 deaths occurred in the United States in 2016. Ninety-five percent of cases in 2016 occurred in someone with at least 1 underlying condition, most commonly obesity (53.9%) and diabetes (53.4%). Resistance to clindamycin increased from 37.0% of isolates in 2011 to 43.2% in 2016 (P = .02). Serotypes Ia, Ib, II, III, and V accounted for 86.4% of isolates in 2016; serotype IV increased from 4.7% in 2008 to 11.3% in 2016 (P < .001 for trend).

CONCLUSIONS AND RELEVANCE The public health burden of invasive GBS disease among nonpregnant adults is substantial and continues to increase. Chronic diseases, such as obesity and diabetes, may contribute.

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Group B *Streptococcus* (GBS) emerged as a leading cause of neonatal sepsis in the 1970s[1] and has been identified as a cause of infection in pregnant and postpartum adults.[2] Since the late 1980s, GBS disease has gained recognition as a significant and increasing cause of severe infections among nonpregnant adults, especially the elderly and those with underlying conditions.[3-17] In particular, obesity and diabetes have been associated with an increased risk of disease.[8,10,16,18]

A previous analysis showed that rates of invasive GBS disease among nonpregnant adults more than doubled between 1990 and 2007 and approached those of invasive pneumococcal disease in adults 65 years or older; approximately 8% of cases resulted in death.[3] There are no current strategies to prevent invasive GBS disease in adults. Vaccines to prevent infant disease are under development and may also hold promise for direct protection of adults at risk for invasive GBS disease.[19-22] We used active, population-based surveillance for invasive GBS disease via the Active Bacterial Core surveillance (ABCs) network to determine the incidence of disease among nonpregnant adults from 2008 to 2016 and to characterize antimicrobial susceptibility and serotype trends.

Key Points

Question What are the key epidemiologic findings and trends in invasive group B *Streptococcus* infections among nonpregnant adults?

Findings In this population-based study of 21 250 patients with invasive group B *Streptococcus* detected by the Active Bacterial Core surveillance network from 2008 through 2016, invasive group B *Streptococcus* incidence among nonpregnant adults increased significantly from 8.1 cases per 100 000 population in 2008 to 10.9 in 2016; incidence was highest among those with male sex, age 65 years or older, and black race. Cases had high rates of obesity (53.9%) and diabetes (53.4%).

Meaning The incidence of invasive group B *Streptococcus* continues to rise among nonpregnant adults; chronic diseases, such as obesity and diabetes, may contribute.

Methods

Population-Based Surveillance

Active, population-based and laboratory-based surveillance for invasive GBS disease in adults was conducted at 10 sites in the United States as part of the Centers for Disease Control and Prevention (CDC) Emerging Infections Program's ABCs as previously described.[23] Briefly, ABCs staff contacted all microbiology laboratories serving patients in the ABCs catchment area. Between January 1, 2008, and December 31, 2016, surveillance was conducted in California (3-county San Francisco Bay area), Colorado (5-county Denver area, 2011-2016 only), Connecticut (entire state, 2016 only), Georgia (20-county Atlanta area), Maryland (entire state), Minnesota (entire state), New Mexico (entire state), New York (15 counties surrounding the Rochester and Albany areas), Oregon (3 counties in the Portland area), and Tennessee (11 counties surrounding Nashville in 2008-2010 and 20 counties surrounding Nashville and Memphis in 2011-2016). The adult population under surveillance ranged from 21.4 million in 2008 to 28.8 million in 2016 (approximately 9.3% and 11.5% of the US adult population, respectively). Demographic and clinical information was abstracted from medical records. The outcome of death was considered GBS associated if it occurred during the hospitalization for invasive GBS; cause of death was not assessed. If the outcome status was unknown during initial medical record review, vital records were used to determine if the patient died during his or her hospitalization for invasive GBS. Laboratory audits were conducted at least yearly to ensure complete case ascertainment.

Activities of the ABCs network are considered part of public health surveillance and have been determined to be nonresearch by CDC's Institutional Review Board. Where required, institutional review board approval for surveillance activities was obtained at ABCs site health departments and academic institutions. Informed consent was not required for this surveillance activity.

Definitions

A case of invasive GBS disease in a nonpregnant adult was defined as GBS isolated from a normally sterile site in a surveillance area resident who was 18 years or older and neither pregnant nor less than 30 days postpartum on the day of culture. Women for whom pregnancy status was missing or unknown were excluded. The GBS disease was considered recurrent if the patient had a positive GBS culture at least 30 days after a prior positive culture and was considered health care associated if GBS was isolated more than 2 days into hospital admission. Patients were classified as residents of long-term care facilities if that was their designated place of residence at the time of initial culture.

Specimen Collection and Testing

Surveillance isolates were forwarded to the *Streptococcus* laboratory at CDC from 6 ABCs sites (Colorado, Georgia, Maryland, Minnesota, New Mexico, and Oregon) throughout the study period and from California (2014-2016 only). From 2008 to 2015, serotyping was performed by latex agglutination using rabbit antisera to 9 GBS capsular polysaccharides (Ia, Ib, and II-VIII); for isolates that could not be typed by latex agglutination, an attempt was made to type by polymerase chain reaction (PCR).[24] If PCR was unsuccessful, the isolate was considered nontypeable. Antimicrobial susceptibility testing to ampicillin, cefazolin, cefotaxime, cefoxitin, ceftizoxime, clindamycin, daptomycin, erythromycin, levofloxacin, penicillin, tetracycline, and vancomycin was performed at CDC by reference broth microdilution, and isolates were classified according to standards established by the Clinical and Laboratory Standards Institute.[25,26] For this report, the term *resistant* was applied to isolates with intermediate or resistant interpretation; for antimicrobials without defined Clinical and Laboratory Standards Institute break points, the term *nonsusceptible* was used. From 2011 to 2015, isolates were also tested for inducible clindamycin resistance by the single-well broth test.[25-28]

Broth microdilution testing was performed by the Minnesota Public Health Laboratory for isolates from Minnesota. The CDC *Streptococcus* laboratory conducted whole-genome sequencing (WGS) for all isolates in 2015 and 2016 and for select isolates from 2008 to 2014. For this analysis, serotypes were assigned using latex agglutination for 2008 to 2014 and predicted from WGS using the CDC bioinformatics pipeline for 2015 and 2016 (https://github.com/BenJamesMetcalf).[29] Antimicrobial susceptibility profiles were also predicted from WGS data for all year 2016 isolates.[29]

Statistical Analysis

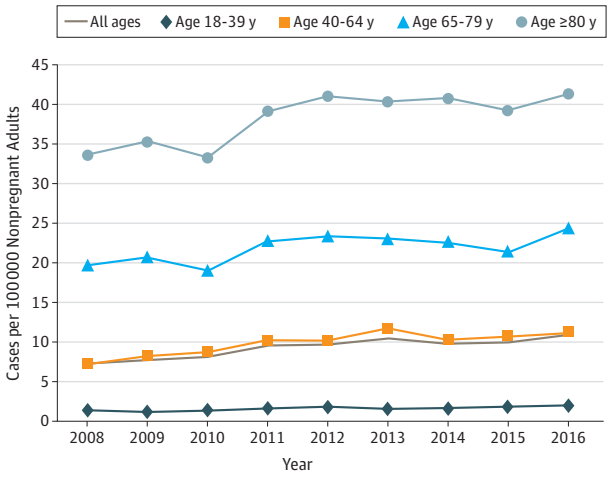
Disease incidence was calculated using case counts from ABCs as numerators and population estimates from the bridged-race vintage postcensal file from the US Census Bureau as denominators. Missing data were multiply imputed by fully conditional specification using Markov chain Monte Carlo methods.[30,31] To obtain national estimates of cases in 2016, age group and race-specific rates of disease were applied from the aggregate surveillance area to the age and racial distribution of the US population for that year. Trends were assessed using the Cochran-Armitage test (2-sided $P < .05$ was considered statistically significant); when data were not linear, we reported the percentage change in incidence or proportion over time or used the nonparametric Mann-Kendall test for trend. Sensitivity analysis showed that incidence trends did not differ markedly when analysis was restricted to cases from regions that were included all years of the study period (91.8% of cases came from these regions); therefore, trends were calculated using all available data for each year. We used body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) to determine obesity (BMI≥30). For patients whose height and weight were in the medical record, BMI was calculated; if height or weight was missing or the calculated BMI was thought implausible (≤12 or >100), BMI was imputed 30 times[32] using a regression model that included sex, age, race, insurance status, year, location, clinical syndrome, presence of underlying conditions, and height (if available) and weight (if available). We used Pearson χ^2 test and 2-tailed Fisher exact test to compare proportions; $P < .05$ was considered statistically significant. Poisson regression models were used to estimate variance for comparisons of incidence rates involving multiply-imputed data. Log binomial models were used to estimate variance for comparisons of proportions involving multiply-imputed data. Standard methods were used to combine estimates from multiply-imputed data sets.[33]

Results

Trends Over Time

A total of 21 250 invasive GBS cases among nonpregnant adults were identified in the ABCs catchment area from 2008 through 2016. The incidence of invasive GBS in nonpregnant adults increased from 8.1 to 10.9 cases per 100 000 population between 2008 and 2016 ($P = .002$ for trend). Incidence increased significantly with age, with the highest incidence observed in persons 80 years or older, who accounted for 17.7% of total cases (**Figure 1**). The overall case fatality rate from 2008 to 2016 was 6.5%, which declined from 7.5% in 2008 to 5.6% in 2016 ($P < .001$ for trend).

Figure 1. Incidence of Invasive Group B Streptococcal Infections Among Nonpregnant Adults



Data are shown for Active Bacterial Core surveillance sites, 2008-2016.

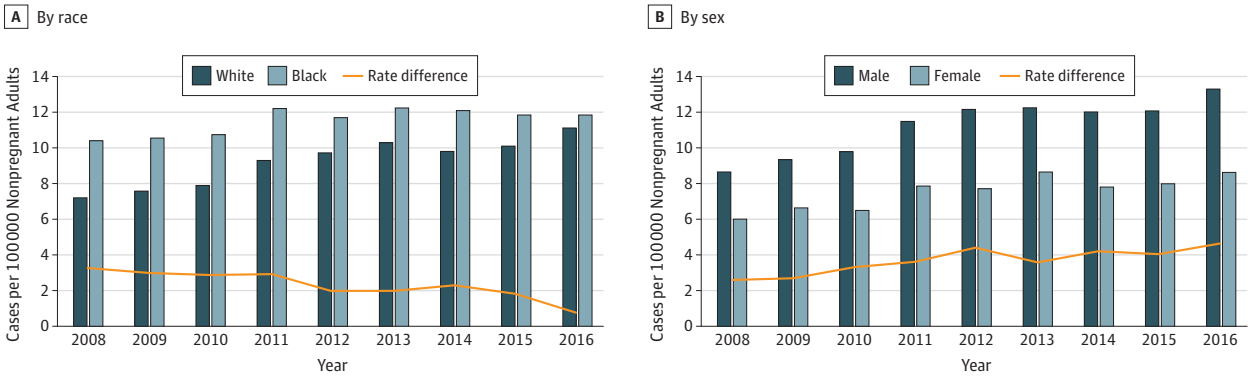
The incidence of invasive GBS disease differed by race and sex across all age groups. Blacks had a significantly higher incidence than whites overall, although the absolute rate difference declined over time, and the difference was no longer significant in 2016 (**Figure 2**A). Men had a significantly higher incidence than women for all years, and this difference grew more pronounced over time (Figure 2B). Overall, the increase was more pronounced among whites, particularly among white men aged 18 to 64 years and 80 years or older and among white women aged 40 to 79 years. Incidence also increased among black men aged 40 to 64 years but decreased among black men 80 years or older. Case fatality rates were higher among blacks than whites (7.4% vs 6.3%; $P = .008$) but were comparable between women and men (6.8% vs 6.3%; $P = .20$).

The percentage of patients with invasive GBS who had at least 1 underlying condition increased from 90.7% in 2008 to 94.6% in 2016 ($P = .005$ for trend). A significant increase between 2008 and 2016 was observed in the percentage of patients with obesity (47.6% to 53.8%; $P = .02$ for trend), diabetes (43.5% to 53.4%; $P < .001$ for trend), heart failure (13.5% to 18.1%; $P < .001$ for trend), and chronic skin disease (9.1% to 17.3%; $P < .001$ for trend); however, the percentage of patients with cancer remained stable (range, 13.5%-16.8%), and the percentage of patients with atherosclerotic cardiovascular disease declined from 23.4% to 20.7%. Among leading clinical syndromes, the percentage of patients with skin and soft-tissue infections (SSTIs) increased from 27.2% in 2008 to 34.0% in 2016 ($P < .001$ for trend).

Descriptive Epidemiology, 2016

There were 3146 GBS cases reported in 2016, corresponding to an estimated 27 729 cases of invasive GBS disease and 1541 deaths in 2016 nationwide. Among ABCs cases, 59% were male,

Figure 2. Incidence of Invasive Group B Streptococcal Infections Among Nonpregnant Adults by Race and Sex



A and B, Data are shown for Active Bacterial Core surveillance sites, 2008-2016.

75% were white, and the median age was 64 years (age range, 18-103 years) (**Table**). Ninety-five percent of patients were admitted to the hospital; 27.3% of those required intensive care, and 5.7% died. Group B *Streptococcus* was isolated predominantly from blood (83.5%), joint (7.7%), and bone (6.3%) specimens. Invasive disease manifested most commonly as SSTIs (34.0%), bacteremia without a focus (32.3%), osteomyelitis (13.3%), pneumonia (10.2%), and septic arthritis (10.2%) (Table). Patients 65 years or older were more likely to have pneumonia and less likely to have osteomyelitis or septic arthritis than younger patients, and they were more likely to have bacteremia without a focus than patients aged 40 to 64 years. Recurrent disease was observed in 7.3% of cases; these cases were significantly more likely to manifest as SSTIs (43.9% vs 33.2%) and to be associated with diabetes (63.0% vs 52.7%), obesity (62.3% vs 51.7%), renal disease (28.7% vs 22.0%), and chronic skin disease (28.7% vs 16.4%) ($P < .05$ for all comparisons).

Ninety-five percent of case patients had at least 1 underlying condition; proportions were similar by sex or race. Obesity and diabetes were the most common underlying conditions, and both conditions were more common among patients aged 40 to 64 years than among older or younger groups. Patients with diabetes were more likely to have SSTIs or osteomyelitis than to have bacteremia without a focus or joint infection compared with nondiabetic patients. Obese patients were more likely to have SSTIs and less likely to have bacteremia without a focus or osteomyelitis than nonobese patients.

Isolate Characteristics

From 2008 to 2016, a total of 13 563 isolates were analyzed for serotype, representing 87.0% of cases from sites collecting isolates. Through 2014, most isolates were serotyped by latex agglutination, with 9.4% tested by PCR. The overall distribution of serotypes changed over the study period (eFigure 1 and eTable 1 in the Supplement), with serotypes Ib, II, and IV becoming more prevalent and serotypes Ia, III, and V becoming less prevalent. Serotypes Ia, Ib, II, III, and V accounted for 86.4% of isolates in 2016; serotype IV increased from 4.7% in 2008 to 11.3% in 2016 ($P < .001$ for trend). Between 2008 and 2016, the incidence of serotype Ib disease doubled from 0.8 to 1.6 cases per 100 000, the incidence of serotype II disease increased by more than 70% from 1.1 to 1.9 cases per 100 000, and the incidence of serotype IV quadrupled from 0.3 to 1.2 cases per 100 000 (**Figure 3**). Together, these 3 serotypes accounted for 75% of the overall increase in incidence among patients for whom serotype information was available. Serotype distribution did not vary consistently between sites (eFigure 2 and eTable 2 in the Supplement).

Among 1953 isolates sequenced in 2016, a total of 83.9% showed resistance to tetracycline (range, 66.5% for serotype IV to 93.0% for Ib), 54.8% showed resistance to erythromycin (range, 39.3% for serotype III to 78.7% for IV) (eFigure 3A and eTable 3A in the Supplement), 43.2% showed resistance to clindamycin (range, 6.6% for serotype Ia to 79.2% for IV) (eFigure 3B and eTable 3B in the Supplement), and 2.3% showed resistance to levofloxacin (most common in serotype Ib at 6.0%). Resistance to erythromycin and clindamycin has been stable since 2013 at approximately 55% and 43%, respectively (**Figure 4**). Resistance to clindamycin increased from 37.0% of isolates in 2011 to 43.2% in 2016 ($P = .02$).

During the study period, 68 of 13 563 isolates (0.5%) had laboratory findings suggestive of nonsusceptibility to 1 or more β-lactam antibiotics, including 48 isolates (0.4%) collected during 2008 to 2015 with elevated minimum inhibitory concentration values and 20 isolates (1.0%) collected during 2016 with a *pbp2x* (GenBank AE009948) gene variant associated with an elevated minimum inhibitory concentration (eTable 4 in the Supplement). In addition, 1 isolate was nonsusceptible to linezolid (from 2014), 3 were nonsusceptible to vancomycin (1 from 2011 described in a 2014 study[34] and 2 from 2016), and none were nonsusceptible to daptomycin.

Among 1957 sequenced isolates from 2016, 170 multilocus sequence typing sequence types (STs) were represented. The most common were ST1 (20.5%; predominantly serotypes V, Ib, and II), ST23 (17.4%; predominantly serotype Ia), ST22 (8.4%; predominantly serotype II), ST19 (7.9%; predominantly serotypes III and V), ST459 (7.6%; predominantly serotype IV), and ST8 (6.5%; predominantly serotype Ib). Among sequenced

Table. Characteristics of Nonpregnant Adults With Invasive Group B Streptococcal Infections, 2016

Variable	All (n = 3146)	18-39 y (n = 239)	40-64 y (n = 1391)	≥65 y (n = 1516)	*P* Value[a]
Male sex, No. (%)	1857 (59.0)	135 (56.5)	872 (62.7)	850 (56.1)	<.001
Age, median, y	64	33	55	75	NA
Race, No. (%)[b]					
White	2365 (75.2)	132 (55.2)	979 (70.4)	1254 (82.7)	<.001
Black	576 (18.3)	85 (35.6)	318 (22.9)	173 (11.4)	<.001
Other	205 (6.5)	22 (9.2)	94 (6.8)	89 (5.9)	.14
Case fatality, No./total No. (%)[c]	176/3127 (5.6)	7/236 (3.0)	70/1383 (5.1)	99/1508 (6.6)	.04
Hospitalized, No./total No. (%)[c]	2957/3127 (94.6)	221/238 (92.8)	1303/1381 (94.3)	1433/1508 (95.0)	.35
Intensive care unit admission	808 (27.3)	57 (25.7)	357 (27.4)	394 (27.4)	.87
Health care associated, No. (%)	241 (7.7)	31 (13.0)	129 (9.3)	81 (5.3)	<.001
Long-term care resident, No. (%)[c]	226 (7.2)	5 (2.0)	51 (3.7)	170 (11.2)	<.001
Recurrent disease, No. (%)	230 (7.3)	17 (7.1)	103 (7.4)	110 (7.3)	.98
Clinical syndrome, No. (%)[d]					
Skin/soft-tissue infection[e]	1071 (34.0)	72 (30.1)	502 (36.1)	497 (32.8)	.07
Bacteremia without focus	1016 (32.3)	82 (34.3)	418 (30.1)	516 (34.0)	.06
Osteomyelitis	418 (13.3)	36 (15.1)	262 (18.8)	120 (7.9)	<.001
Pneumonia[f]	322 (10.2)	9 (3.8)	87 (6.3)	226 (14.9)	<.001
Septic arthritis	321 (10.2)	13 (5.4)	173 (12.4)	135 (8.9)	<.001
Septic shock	296 (9.4)	20 (8.4)	122 (8.8)	154 (10.2)	.37
Abscess	202 (6.4)	26 (10.9)	102 (7.3)	74 (4.9)	<.001
Intra-abdominal infection[g]	97 (3.1)	15 (6.3)	58 (4.2)	24 (1.6)	<.001
Endocarditis	65 (2.1)	9 (3.8)	18 (1.3)	38 (2.5)	.01
Meningitis	34 (1.1)	4 (1.7)	19 (1.4)	11 (0.7)	.12
Necrotizing fasciitis	15 (0.5)	1 (0.4)	13 (0.9)	1 (0.1)	.002
Other[h]	169 (5.4)	15 (6.3)	59 (4.2)	95 (6.3)	.04
Unknown	63 (2.0)	13 (5.4)	30 (2.2)	20 (1.3)	<.001
Underlying condition, No. (%)					
≥1 Condition	2977 (94.6)	216 (90.4)	1323 (95.1)	1438 (94.9)	.01
Obesity[i]	1695 (53.9)	116 (48.5)	843 (60.6)	736 (48.5)	<.001
Diabetes	1681 (53.4)	100 (41.8)	805 (57.9)	776 (51.2)	<.001
Neurologic disease[j]	829 (26.4)	41 (17.2)	311 (22.4)	477 (31.5)	<.001
Renal disease[k]	708 (22.5)	31 (13.0)	252 (18.1)	425 (28.0)	<.001
Atherosclerotic cardiovascular disease	650 (20.7)	8 (3.3)	176 (12.7)	466 (30.7)	<.001
Heart failure	570 (18.1)	5 (2.1)	167 (12.0)	398 (26.3)	<.001
Chronic skin disease	545 (17.3)	47 (19.7)	241 (17.3)	257 (17.0)	.59

(continued)

Table. Characteristics of Nonpregnant Adults With Invasive Group B Streptococcal Infections, 2016 (continued)

Variable	All (n = 3146)	18-39 y (n = 239)	40-64 y (n = 1391)	≥65 y (n = 1516)	P Value[a]
Cancer[l]	514 (16.3)	13 (5.4)	167 (12.0)	334 (22.0)	<.001
Chronic obstructive pulmonary disease	405 (12.9)	2 (0.8)	133 (9.6)	270 (17.8)	<.001
Current smoker	362 (11.5)	43 (18.0)	236 (17.0)	83 (5.5)	<.001
Immunosuppression[m]	252 (8.0)	19 (7.9)	119 (8.6)	114 (7.5)	.59
Asthma	233 (7.4)	22 (9.2)	123 (8.8)	88 (5.8)	.004
Liver disease	229 (7.3)	17 (7.1)	148 (10.6)	64 (4.2)	<.001
Alcoholism	219 (7.0)	16 (6.7)	145 (10.4)	58 (3.8)	<.001
Substance abuse[n]	217 (6.9)	44 (18.4)	152 (10.9)	21 (1.4)	<.001
Dialysis	125 (4.0)	14 (5.9)	74 (5.3)	37 (2.4)	<.001

Abbreviation: NA, not applicable.

[a] For the comparison of results among the groups of cases in patients aged 18 to 39 y, 40 to 64 y, and 65 y or older.

[b] Unknown race distributed based on knowns.

[c] The denominators used to calculate percentages were numbers of case patients with known outcome, hospitalization status, or residence.

[d] Case patients may have had more than 1 syndrome (overall, 785 [25.0%] had >1 clinical syndrome), except in the case of Bacteremia without focus, which was only considered to have occurred when no other syndrome was present.

[e] Skin infections included cellulitis, wound, gangrene, skin ulcer, and skin abscess.

[f] Pneumonia includes empyema and/or positive pleural fluid culture.

[g] Intra-abdominal infection includes peritonitis/positive peritoneal fluid culture, intra-abdominal abscess, or specified infection of the pancreas, liver, intestine, or gallbladder.

[h] Other clinical syndromes included upper or lower urinary tract infection (n = 129), pelvic infection (n = 14), scrotal infection (n = 7), endometritis (n = 5), central nervous system infection (n = 4), infection of an indwelling or implanted medical device (n = 3), infected hematoma (n = 3), phlebitis or other vascular infection (n = 3), sinusitis (n = 2), and pericarditis (n = 2).

[i] Obesity status was estimated using multiple imputations (9.3% imputed data).

[j] Neurologic disease includes multiple sclerosis, neuromuscular disease, Parkinson disease, history of stroke, peripheral neuropathy, paraplegia, dementia, seizure disorder, or cerebrospinal fluid leak.

[k] Renal disease includes chronic kidney disease, chronic renal insufficiency, chronic renal failure, and chronic dialysis.

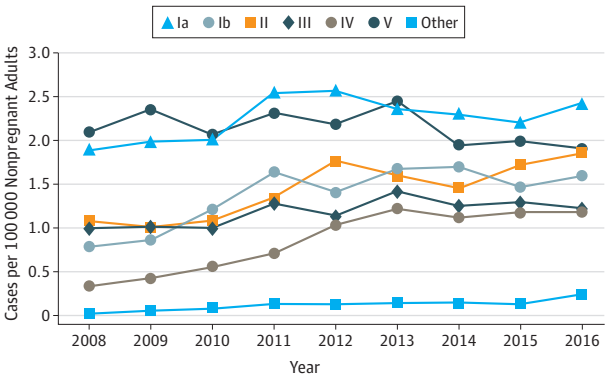
[l] Cancer includes Hodgkin and non-Hodgkin lymphoma, leukemia, multiple myeloma, and solid organ tumor.

[m] Immune suppression includes HIV/AIDS, complement deficiency, immunoglobulin deficiency, immunosuppressive therapy, organ transplant, and splenectomy and/or asplenia.

[n] Substance abuse included prior injection drug use (1.2% of total patients), current injection drug use (1.0%), prior noninjection drug use (1.3%), or current noninjection drug use (4.8%).

isolates containing resistance determinants, resistance to tetracyclines was largely due to the presence of the *tetM* (GenBank HG799494) gene (95.3% of isolates). Resistance to macrolides and lincosamides was due to an *ermB* (GenBank HG799494) gene in 34.9% of isolates, an *ermTR* (GenBank CP002121) gene in 33.1%, and a *mef* (GenBank CP000921) gene in 22.9%. Resistance to fluoroquinolones was typically due to mutations in the quinolone resistance-determining regions of *gyrA* (GenBank CP007571) (49%) or *parC* (GenBank CP007571) (51%). The virulence gene *hvgA* (GenBank CP022537) was present in 77 (3.9%) of isolates, 73 of which were serotype III and a part of the ST17 clonal complex; of the remainder, 1 was serotype III but a part of the ST23 clonal complex, and 3 were serotype IV (2 ST17 clonal complex and 1 ST23 clonal complex).

Figure 3. Incidence of Invasive Group B Streptococcal Infections Among Nonpregnant Adults by Serotype



Data are shown for Active Bacterial Core surveillance (ABCs) sites, 2008-2016. Other serotypes include Ic, VI, VII, VIII, IX, and nontypeable isolates.

Discussion

The incidence of invasive GBS disease among nonpregnant US adults continues to rise, roughly tripling between 1990 and 2016 (from 3.6 to 10.9 cases per 100 000).[3] Given the severity of invasive GBS (94.6% of cases were hospitalized, 27.3% of cases required intensive care unit admission, and 5.6% of cases were fatal in 2016), this rise represents a clinical and public health concern. Incidence is rising disproportionately among certain demographic groups, particularly whites, men, and adults aged 40 to 64 years. The difference in incidence between black and white participants has declined markedly, while the difference between men and women continues to grow; this factor may be related to higher rates of important underlying conditions among men, such as diabetes or smoking. Incidence remains highest among blacks, men, and those 80 years or older. In 2016, the incidence rate of invasive GBS was 60% higher than the rate of invasive group A streptococcal infections and 20% higher than the rate of invasive pneumococcal infections among all adults, and the differences in rates were more pronounced in older age groups.[35,36] The latter may be due to improvements in 13-valent pneumococcal conjugate vaccine coverage among adults 65 years or older or herd immunity from infant vaccination. The incidence of invasive GBS appears to be higher than the incidence of community-acquired methicillin-resistant *Staphylococcus aureus* but lower than the incidence of hospital-acquired methicillin-resistant *Staphylococcus aureus* among adults 65 years or older.[37]

Surveillance data do not allow us to determine the direct cause of the rising incidence. However, the data suggest that the increase may be associated with certain serotypes because serotypes Ib, II, and IV accounted for three-quarters of the increase in incidence between 2008 and 2016. Increasing prevalence of underlying health conditions associated with invasive GBS likely also contributes. A 2014 study[38] linked obesity and diabetes to an increased risk of invasive GBS infections. Our analysis found an increasing prevalence of obesity and diabetes among patients with invasive GBS over the study period. Both obesity and diabetes have been linked to increased risk for SSTIs,[39,40] a syndrome that showed significant gains during the study period. An aging US population may also have contributed to the rise, but the greatest relative increase in incidence rates occurred among those aged 40 to 64 years.

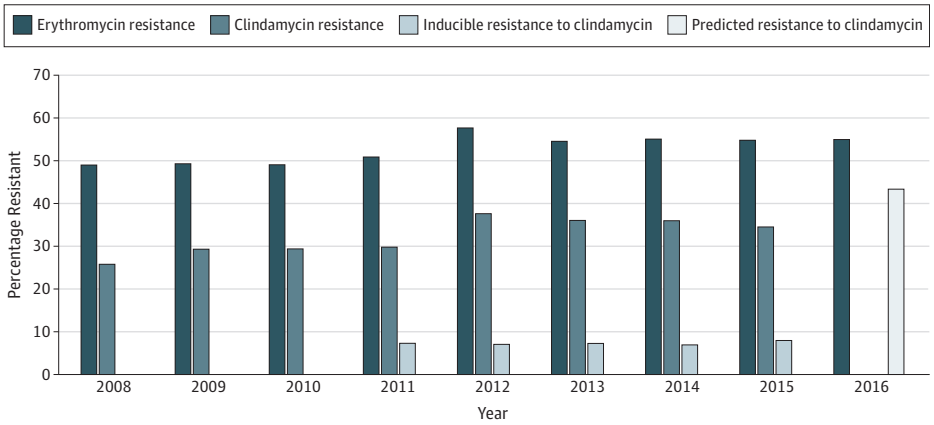
Group B *Streptococcus* remains highly susceptible to β-lactams and vancomycin; however, rare examples of resistance to both have been documented from multiple geographic areas, and their emergence should be monitored.[29,34] Resistance to erythromycin and clindamycin was higher than previously reported[3] and increased over the study period; most of this increase was due to resistance in emerging serotypes Ib and IV. Clinician awareness of trends in antimicrobial resistance of GBS is important when susceptibility results are not available and empirical therapy is necessary. Rising clindamycin resistance is of particular clinical significance in the setting of SSTIs, where clindamycin is often considered a first-line antimicrobial agent.[41]

Multivalent vaccines to prevent infant disease through maternal immunization are under development, and several have entered clinical trials.[19-22,42] Such vaccines may also hold potential for reducing GBS disease in the adult population. There are some data suggesting that adults can mount an immune response to vaccines targeting GBS capsular polysaccharides,[43] but whether they would be effective at preventing invasive GBS in adults, particularly those 80 years or older and those with significant underlying conditions, needs to be determined. Although a pentavalent vaccine containing the most common serotypes (Ia, Ib, II, III, and V) would currently cover 86.4% of nonpregnant adult cases, the recent rise in serotype IV has prompted consideration for including this serotype in vaccine development. The emergence of serotype IV could demonstrate a rise and sustained increase similar to that observed with serotype V disease in nonpregnant adults.[14]

Limitations

This study has several limitations. We did not have denominators to calculate incidence rates by underlying conditions, so we could not directly assess risk posed by common conditions, such as obesity and diabetes, but prevalences of these conditions among GBS cases were much higher than the US adult population (diabetes is estimated to be 12% to 14%[44] and obesity 36%[45] among adults). We excluded female cases missing pregnancy status (89 of 21 250 [0.5% of all cases]), which

Figure 4. Resistance of Invasive Group B Streptococcal Isolates to Erythromycin and Clindamycin Over Time



Data are shown for Active Bacterial Core surveillance sites, 2008-2016. In 2008 to 2010, conventional antimicrobial susceptibility testing without clindamycin inducible-resistance testing was performed. In 2011 to 2015, both conventional antimicrobial susceptibility testing and clindamycin inducible-resistance testing were performed; inducible clindamycin resistance accounted for 6.8% to 7.2% of the total. In 2016, resistance was determined based on the presence of resistance genes in sequenced isolates (the presence of a resistance gene predicts total clindamycin resistance).

likely had only a small influence on the overall incidence and case characteristics. We included all cases in trend analyses, which may have differed slightly from analyses than if we had included only cases from catchment areas common to all years of the study. The focus of this study was limited to invasive GBS disease. Group B *Streptococcus* also causes a substantial burden of noninvasive disease, including urinary tract infections, noninvasive SSTIs, and pneumonia, so the overall burden in adults is likely much higher.[10,46-48]

Conclusions

In summary, the incidence of invasive GBS in nonpregnant adults continues to rise, with rates now exceeding those for invasive pneumococcal disease. The rise parallels an increasing prevalence of underlying conditions, such as obesity and diabetes, and was associated with serotypes Ib, II, and IV. Increasing resistance to clindamycin is also a concern given its clinical use in the management of SSTIs, a common manifestation of GBS disease. A multivalent vaccine could target a substantial portion of adult disease but would be most influential if it included serotype IV, as well as the other major serotypes. Ongoing surveillance to monitor future trends in serotype distribution and antibiotic resistance is warranted. Improved physician awareness and efforts aimed at reducing risk factors, such as obesity and diabetes, along with efforts to maintain skin integrity and provide optimal wound care, may help prevent invasive GBS infections.

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Invited Commentary

Group B *Streptococcus*, an A-List Pathogen in Nonpregnant Adults

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Group B *Streptococcus* (GBS) is a frequent colonizer of the human gastrointestinal tract, gynecological tract, and skin. It has been recognized as a major cause of infections in pregnant women and neonates since the 1970s. In nonpregnant adults, sporadic case reports of GBS infections date back to the 1940s, shortly after the serological classification of hemolytic streptococci into groups.[1] However, only recently has GBS been recognized as a major cause of infections in this population.

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Intensive population-based surveillance programs of GBS began in the late 1980s,[2] and infection rates in nonpregnant adults have risen steadily in subsequent years.[3] With the decreasing rates of infection in neonates owing to the implementation of guidelines for intrapartum antibiotic prophylaxis in the mid-1990s, the vast majority of invasive GBS disease and GBS-associated mortality in the United States now afflicts the nonpregnant adult population.

While GBS may be less familiar to these adults and their clinicians than group A *Streptococcus* and *Streptococcus pneumoniae*, active surveillance efforts on the part of the Centers for Disease Control and Prevention have demonstrated that GBS now causes more adult infections than these other streptococcal species in the United States. Because internists are responsible for preventing, diagnosing, and treating the majority of GBS infections in our population, tracking the epidemiology of these infections is critically important, especially as surveillance efforts are waning in other parts of the world.[4]

In this issue of *JAMA Internal Medicine*, Francois Watkins and colleagues[5] at the Centers for Disease Control and Prevention provide a concerning update regarding the increasing rates of GBS infections in nonpregnant adults using data from 2008 to 2016. They report that rates of infection continued to increase—from 8.1 cases per 100 000 population in 2008 to 10.9 cases per 100 000 population in 2016—roughly triple the rate from 1990. They found higher rates among men than women and among blacks than whites, as well as increased risk with age, rising to more than 40 cases per 100 000 in patients 80 years and older.

Projected to the US population, they estimate that 27 729 cases of invasive GBS disease and 1541 deaths occurred in the United States in 2016, with a case-fatality rate of 5.6%.[5] The most common clinical syndromes were skin and soft-tissue infections (SSTIs), bacteremia without a focus, osteomyelitis, pneumonia, and septic arthritis. The majority (95%) of cases in 2016 occurred in patients with at least 1 underlying comorbidity, most commonly diabetes (53%) and obesity (54%). Also, rates of clindamycin resistance increased from 37% of isolates in 2011 to 43% in 2016.

These results provide guidance for how internists should think about GBS when evaluating patients with signs of infection. First, GBS infections may be difficult to identify before results of culture data because the exposure history and infection syndromes may be nonspecific. Because GBS is a common colonizer that can also cause infections, no unusual epidemiologic exposures are required for GBS infections. Group B *Streptococcus* can cause a range of infection syndromes, including SSTIs, pneumonia, osteomyelitis, bacteremia without a source, septic arthritis, endocarditis, and others. Because the clinical syndromes generally are not unique to GBS, it is critical to collect cultures that will help make the diagnosis.

Second, the most helpful clues in assessing a patient for GBS infection are the patient's age and comorbidities: the risks of infection rise with age, and the vast majority of GBS infec-