MAJOR ARTICLE

Epidemiology of Invasive Group A *Streptococcus* Disease in the United States, 1995–1999

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Severe invasive group A streptococcal (GAS) disease is believed to have reemerged during the past 10–20 years. We conducted active, laboratory, population-based surveillance in 5 US states (total population, 13,214,992). From 1 July 1995 through 31 December 1999, we identified 2002 episodes of invasive GAS (3.5 cases per 100,000 persons). Rates varied by age (higher among those <2 or ⩾65 years old), surveillance area, and race (higher among black individuals) but did not increase during the study period. The 5 most common *emm* types (1, 28, 12, 3, and 11) accounted for 49.2% of isolates; newly characterized *emm* types accounted for 8.9% of isolates. Older age; presence of streptococcal toxic shock syndrome, meningitis, or pneumonia; and infection with *emm1* or *emm3* were all independent predictors of death. We estimate that 9600–9700 cases of invasive GAS disease occur in the United States each year, resulting in 1100–1300 deaths.

Group A *Streptococcus* (GAS) causes invasive, noninvasive, and nonsuppurative diseases. Invasive GAS infections include, among others, bacteremia, pneumonia, puerperal sepsis, necrotizing fasciitis (NF), and streptococcal toxic shock syndrome (STSS) [1, 2]. Nonsuppurative GAS diseases, acute rheumatic fever, and poststreptococcal glomerulonephritis are now uncommon in the United States; however, outbreaks do occur, and such diseases remain important causes of morbidity and mortality globally [3–16].

Beginning in the 1980s, reports suggested a shift in the epidemiology of GAS disease toward the occurrence of more-severe clinical illness [17–22]. The first modern era report of GAS causing a toxic shock–like syndrome was published in the Czechoslovakian literature in 1984 [19, 23], followed by numerous reports from the United States and Europe [18, 21, 24, 25]. The only population-based study from the United States at that time also concluded that a toxic shock–like syndrome caused by GAS had emerged [26]. Subsequently, a case definition for this condition was established [27]. Contemporaneously, laboratory studies revealed an increase in isolates that expressed M protein types 1 and 3 [28, 29]. Hospital-based reports suggested that the occurrence of more-severe GAS disease was accompanied by increases in GAS disease incidence [15, 25, 30, 31], but such an increase was not found in the only available population-based surveillance study [26]. Indeed, the

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annual rate of invasive GAS disease among defined populations in the United States has been documented to range from 2.6 to 6.8 cases per 100,000 persons, and fluctuations in the annual incidence are certain to exist [17]. The absence of longitudinal population-based surveillance covering large populations in the United States has limited generalizations about real trends in the incidence of invasive GAS infection and in the characteristics of the organism itself.

Methods to prevent or control GAS disease have been limited and currently center on accurate diagnosis and timely, appropriate use of antimicrobial therapy. New efforts at disease prevention are focused on vaccine development, an important component of which involves the accurate assessment of the disease burden and characterization of disease-causing isolates.

In the present article, we describe the burden and *emm* type distribution of invasive GAS infections in the United States between 1995 and 1999 that were found using population-based active surveillance. Our goals were to determine whether invasive GAS infections have increased in incidence and to provide strain information that can be used in vaccine development.

MATERIALS AND METHODS

Surveillance. We conducted population-based, active laboratory surveillance for invasive *Streptococcus pyogenes* (GAS) from 1 July 1995 through 31 December 1999 in the following regions: Atlanta, Georgia (Cobb, Clayton, Dekalb, Douglas, Fulton, Gwinnett, Newton, and Rockdale counties); Minneapolis/St. Paul, Minnesota (Anoka, Carver, Dakota, Hennepin, Ramsey, Scott, and Washington counties); Portland, Oregon (Clackamas, Multnomah, and Washington counties); the San Francisco Bay area, California (Alameda, Contra Costa, and San Francisco counties); and all of Connecticut. The estimated 1999 aggregate population was 13,214,992 (4.8% of the US population). All clinical microbiology laboratories that processed cultures of samples from normally sterile sites were contacted at least monthly, laboratory records were searched for cases, and audits were conducted every 6 months to identify missed cases. A case was defined by the isolation of GAS from a normally sterile site in a resident of the surveillance area or isolation of GAS from a nonsterile site (e.g., wound culture) in conjunction with NF. This study was reviewed by the Institutional Review Boards of the Centers for Disease Control and Prevention and participating institutions. US Department of Health and Human Services guidelines for conduct of studies were followed.

Clinical syndromes and underlying disease information were determined by chart review or reports from infection-control practitioners. Case patients who had positive results of blood culture for GAS but for whom no clinical syndrome was identified were categorized as having only bacteremia without a source; for all other case patients, data could be categorized under multiple clinical syndromes. Surveillance sites identified case patients as having STSS by reviewing the charts and assessing whether the published case definition was met [27] or by noting that a diagnosis of STSS had been made by the treating physician, with or without fulfillment of the case definition. Case patients were categorized as having NF if this diagnosis was documented in the chart (with or without confirmation by pathologic examination) or if necrosis of tissue was noted on a pathologic or surgical report. Skin and soft-tissue infections included cellulitis, infected ulcers, erisypelas, wound infections, lymphangitis, lymphadenitis, phlebitis, bursitis without a positive culture of joint fluid for GAS, and tenosynovitis but excluded NF. Nosocomial acquisition was presumed to have occurred if the culture was done $\geqslant$3 days after admission.

GAS typing. GAS isolates were sent to the Centers for Disease Control and Prevention (CDC) for identity confirmation and typing. Isolates were typed on the basis of opacity factor reaction, T typing, and sequencing of the variable M protein type–specific region of *emm* gene amplicons [32–35]. A near-absolute concordance has been established between the 5′ *emm* variable region sequence type and M serotype [33, 34, 36, 37]; a listing of types can be found at http://www.cdc.gov/ncidod/biotech/infotech_hp.html. We considered any type other than *emm* types 1–93 to be a newly characterized type—these likely represented some of those types that were listed elsewhere as nontypeable when rabbit antisera were used.

Descriptive epidemiology. Descriptive analyses were conducted that included all cases with onset from 1 July 1995 through 31 December 1999. Incidence calculations included only those cases with onset from 1 January 1996 through 31 December 1999. We used regional and national postcensus population estimates for each year as the denominator values. National estimates of the incidence of cases and the number of deaths due to GAS were calculated by multiplication of the aggregate age- and race-specific incidence in the surveillance areas by the population figures for the United States. Individuals of unknown race (44 in 1996, 53 in 1997, 54 in 1998, and 88 in 1999) were assigned to racial groups on the basis of the proportion observed among those with known race. Case-fatality ratios (CFRs) were calculated on the basis of the number of cases for which the outcome was known (99.3%).

Multivariable models. Risk factors for death were evaluated by use of univariate and multivariable analyses. All variables associated with death in a univariate analysis, as well as age group and race data, were included in a Poisson regression model in which death was the outcome variable. Mutually exclusive clinical syndromes, in descending order of CFR (i.e., STSS, meningitis, pneumonia, NF, bacteremia without a source,

abdominal/peritoneal infection, cellulitis, osteomyelitis, and septic arthritis), and *emm* type (i.e., type 1, type 3, or other *emm* types) were covariates. Case patients with multiple clinical syndromes were classified in the category of highest severity. The model was restricted to cases for which information on all variables was available; thus, cases caused by GAS with unknown *emm* types ($n = 411$) and for which the outcome was unknown ($n = 14$) were excluded. All 2-way interactions were evaluated. Variables were considered to be associated with death at $\alpha < .05$. All univariate and multivariable analyses were conducted by use of SAS software (version 8 for Windows).

RESULTS

Disease rates. From 1 July 1995 through 31 December 1999, 2002 cases of invasive GAS disease were identified in 2002 patients in the 5 surveillance areas. The average annual incidence of invasive GAS disease for these years was 3.5 cases per 100,000 persons. The incidence of disease varied by area, from 2.2 to 4.8 cases per 100,000 persons (in Georgia and California, respectively), but did not vary significantly from year to year in any individual area (table 1). The overall incidence varied by season, with the preponderance of disease occurring in the winter and early spring (figure 1).

The incidence varied substantially by race and age (figure 2). The incidence was highest among those ⩾65 years old (9.3 cases per 100,000 persons), followed by those <2 years old (6.3 cases per 100,000 persons). Infection was 1.6 times more likely to occur among black persons than among those of other race (95% CI, 1.4–1.7). Age- and race-adjustment of the surveillance data to the US population yielded an annual incidence of 3.6 cases per 100,000 people, or an estimated 9600–9700 annual cases. The incidence of GAS-associated NF and STSS varied by year, surveillance area, and age group; however, no consistent increase or decrease in disease incidence was evident across any of these strata.

Underlying diseases. The proportion of patients who had cases of invasive GAS disease 1998 and 1999 and had various underlying diseases is shown in table 2. Underlying disease information was collected for 577 (74.1%) of the 779 cases that had onset during these 2 years; underlying disease information for Georgia was not reported for this period of surveillance. HIV infection was more commonly reported among case patients in California than among case patients in the other 3 states for which this information was available (RR, 4.8; $P < .001$). Injection drug use was more commonly reported among case patients from Oregon and California than among case patients from Connecticut and Minnesota (RR, 5.0; $P < .001$). After exclusion of those patients with HIV infection or a history of injection drug use, there were no substantial differences in the proportion of case patients with an underlying disease by surveillance area (Connecticut, 84.4%; Oregon, 83.0%; California, 76.6%; and Minnesota, 76.2%). Overall, 82.7% (range, by geographic region, 77.3%–86.8%) of case patients with invasive GAS disease had at least 1 underlying condition. Varicella was noted in 5 (6.3%) of 79 case patients <10 years old and only 4 (0.6%) of 700 patients ⩾10 years old.

Clinical syndromes. The distribution of clinical syndromes among age groups is shown in table 3. Compared with those age ⩾10 years, those age <10 years were less likely to present with a cutaneous/soft-tissue infection, NF, STSS, or endocarditis/pericarditis and were more likely to present with bacteremia without a source, osteomyelitis, or a CNS infection. Pregnancy-related infections accounted for 36 (1.8%) of all invasive GAS cases.

The overall CFR for invasive GAS disease was 12.5%. CFRs varied substantially by age and clinical syndrome (table 3; figure 2). Case patients <30 years old were at extremely low risk of death; risk of death increased with each age category ($P < .001$; χ^2 test for trend). The highest CFR was observed among case patients with STSS (44.5%). Among those with NF, the CFR varied substantially, depending on whether the patient also

Table 1. Incidence of invasive group A *Streptococcus* (GAS) disease, by region and year, in the United States, 1 January 1996 through 31 December 1999.

	Incidence of invasive GAS disease, cases per 100,000 people					
Region	1996	1997	1998	1999	Overall	Adjusted[a]
California	4.48	4.03	3.92	4.78	4.30	4.56
Connecticut	3.70	3.61	3.18	3.26	3.44	3.35
Georgia	2.23	2.74	2.81	2.17	2.49	2.36
Minnesota	3.64	3.70	4.17	3.96	3.87	4.73
Oregon	3.38	3.79	3.52	3.33	3.50	3.88
All 5 states	3.52	3.55	3.50	3.52	3.52	3.59
United States (projected incidence)	3.62	3.63	3.57	3.56	3.59	—

[a] Overall incidence, adjusted for age and race.

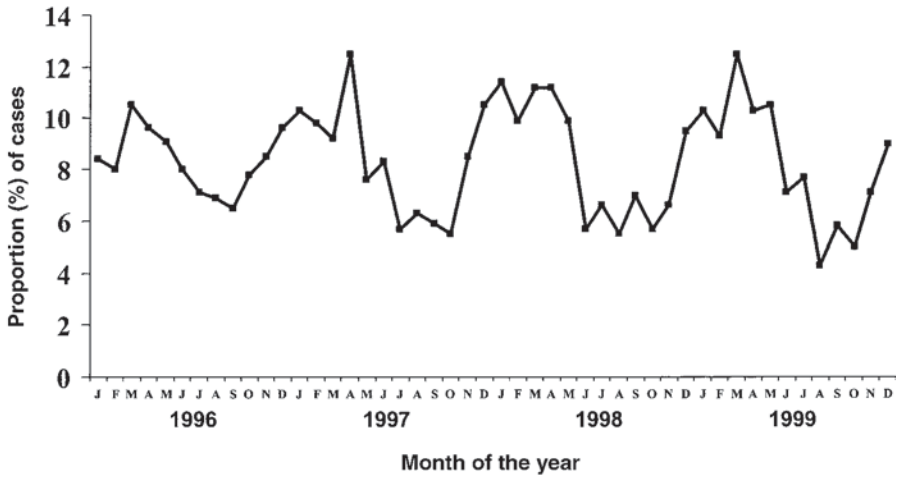

Figure 1. Monthly distribution of invasive group A *Streptococcus* disease in 5 regions in the United States, 1 January 1996 through 31 December 1999.

had STSS (41.4% for case patients with STSS and 22.1% for those without STSS). Among patients with neither STSS nor NF, the CFR was 10.1%.

Of the 2002 cases included in our study, GAS was isolated from blood samples in 1485 (74.2%). Among the 517 (25.8%) case patients without documented bacteremia, GAS was isolated from surgical specimens (234 case patients [11.7%]), joint fluid (167 case patients [8.3%]), peritoneal fluid (37 case patients [1.8%]), pleural fluid (36 case patients [1.8%]), bone (17 case patients [0.8%]), CSF (14 case patients [0.7%]), wound specimens (6 case patients [0.3%]), abscess specimens (4 case patients [0.2%]), pericardial fluid (1 case patient [0.05%]), and fluid from the uterus (1 case patient [0.05%]). One hundred nine (5.4%) of the 2002 cases were categorized as having been nosocomially acquired. Of the cases that were related to pregnancy, 5 (13.9%) were categorized as having been nosocomially acquired.

emm *sequence types.* Of the 2002 cases included in our study, isolates from 1586 (79.2%) were available for evaluation. In the remaining cases, isolates were not obtained, did not survive, or (in a small number of cases) did not produce PCR product. Among those 1586 isolates, the 10 most common *emm* types were types 1 (20.8%), 28 (9.2%), 12 (7.6%), 3 (7.1%), 11 (4.5%), 4 (4.1%), 114 (3.9%), 89 (3.2%), 77 (3.1%), and 33 (2.5%). The 5 most common types accounted for 49.5% of isolates, and the 10 most common types accounted for 66.0% of isolates identified; 80% of isolates were accounted for by 17 different *emm* types. The proportion of disease caused by each type varied over the course of time and by surveillance area (data not shown). Only *emm* types 1, 28, 12, 3, and 11 ranked among the 10 most common in all surveillance areas for the 1995–1999 time period.

Newly characterized *emm* types accounted for 8.9% of isolates evaluated. One of these, *emm114* [38, 39], ranked as the second most common type identified in California, the third most common in Oregon, and seventh most common overall.

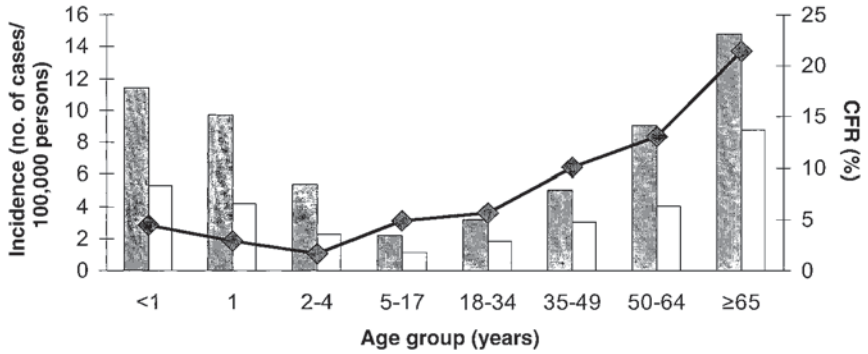

Figure 2. Incidence of invasive group A *Streptococcus* disease, by age and race. Age-specific case-fatality ratio (CFR) for all races combined is shown by the black line. *Dark columns,* black race; *light columns,* other race.

Table 2. Underlying conditions reported among case patients with invasive group A *Streptococcus* disease in 1998 and 1999, by surveillance area.

Underlying condition[a]	No. (%) of case patients with underlying condition				
	Total (n = 577)	In California (n = 221)	In Connecticut (n = 152)	In Minnesota (n = 128)	In Oregon (n = 76)
HIV/AIDS	20 (3.5)	15 (6.8)	1 (0.7)	4 (3.1)	0 (0)
Injection drug use	75 (12.9)	46 (20.8)	10 (6.6)	2 (1.6)	17 (22.4)
Alcohol abuse	97 (16.8)	39 (17.6)	18 (11.8)	25 (19.5)	15 (19.7)
Diabetes mellitus	125 (21.6)	30 (13.6)	44 (28.9)	29 (22.7)	22 (28.9)
Undergoing dialysis	48 (8.3)	11 (5.0)	13 (8.6)	11 (8.6)	13 (17.1)
Immunosuppression[b]	13 (2.3)	7 (3.2)	2 (1.3)	2 (1.6)	2 (2.6)
Chronic obstructive pulmonary disease	56 (9.7)	14 (6.3)	20 (13.2)	11 (8.6)	11 (14.5)
Heart disease[c]	140 (24.3)	33 (14.9)	58 (38.2)	25 (19.5)	24 (31.6)
Malignancy[d]	97 (16.8)	33 (14.9)	34 (22.4)	17 (13.3)	13 (17.1)
Cirrhosis	20 (3.5)	9 (4.1)	8 (5.3)	1 (0.8)	2 (2.6)
Skin abnormality[e]	10 (1.7)	2 (0.9)	3 (2.0)	3 (2.3)	2 (2.6)
Asplenia/sickle cell disease	4 (0.7)	0 (0)	0 (0)	2 (1.6)	2 (2.6)
No underlying illness	100 (17.3)	39 (17.6)	22 (14.5)	29 (22.7)	10 (13.2)

[a] Some case patients had >1 underlying condition.
[b] Resulting from immunoglobulin deficiency or treatment associated with systemic lupus erythematosus, nephrotic syndrome, or organ transplantation.
[c] Heart and atherosclerotic cardiovascular disease.
[d] Leukemia, myeloma, Hodgkin disease, or other malignancies.
[e] Burns or varicella.

Predictors of clinical syndromes. We evaluated the association between *emm* type and the presence of various clinical syndromes. In a univariate analysis, *emm1* strains were associated with STSS (RR, 2.0; $P < .001$) and pneumonia (RR, 1.7; $P < .001$); *emm3* strains, with STSS (RR, 2.7; $P < .001$) and NF (RR, 2.9; $P < .001$); and *emm28* strains, with pregnancy-related infections (RR, 4.3; $P < .001$). We also evaluated whether the presence of underlying conditions was a predictor of clinical syndrome and found that individuals with STSS were more likely than those without STSS to have at least 1 underlying medical condition (94.9% vs. 81.8%, respectively; RR, 1.2; $P = .04$).

In a multivariable Poisson regression analysis, we assessed predictors of death (table 4). When the analysis was controlled for race, we found that increasing age, disease syndrome (pneumonia, meningitis, or STSS), and *emm* type (types 1 and 3) were all independent predictors of death.

DISCUSSION

The results of our population-based, active surveillance of 5 regions in the United States demonstrate that the incidence of invasive GAS infections was stable between 1996 and 1999. Compared with incidence rates of GAS infection reported by hospital-based or small regional studies done during the 1980s and 1990s, there has been no apparent increase in the incidence since the 1980s. It has been suggested that a transient increase in incidence occurred in the mid- to late 1980s [40]. However, by combining our results for the incidence of invasive GAS disease in Georgia (2.2 cases per 100,000 persons) with those of a 1994–1995 report from the same area (5.2 cases per 100,000 persons) [41], it is evident that variations in the incidence of invasive GAS disease within a region over the course of short periods of time do occur. This likely reflects a combination of the population's susceptibility to particular *emm* types and variation in the predominant *emm* types circulating within a community. The relative importance of any individual *emm* type in the proportion of invasive disease it causes is likely a combination of the relative frequency of strain circulation within a community, the invasiveness of that strain, and the degree of individual and population-level immunity to that strain. Without contemporaneous data on the prevalence of *emm* strains that circulate in the community but do not cause disease, no conclusions can be drawn about the relative invasiveness of a strain.

In all geographic areas and for all time periods, the incidence of invasive GAS disease among black individuals was higher than the incidence among those of other race. The source of this disparity in incidence is not clear, but the disparity may be due to differences in the prevalence of underlying diseases, socioeconomic conditions, or other, as-yet-uncharacterized risk factors.

Invasive GAS disease results in significant morbidity and mortality. We estimate that, each year in the United States,

Table 3. Clinical syndromes among case patients with invasive group A *Streptococcus* disease, by age group, and all-age case-fatality ratios (CFRs), 1 July 1995 through 31 December 1999.

Syndrome[a]	No. (%) of case patients with syndrome				Overall CFR, %
	All (n = 2002)	Age <10 years (n = 226)	Age ⩾10 years (n = 1776)	P[b]	
Cutaneous/soft-tissue infection	742 (37.1)	44 (19.5)	698 (39.3)	<.001	7.4
Bacteremia without a source	567 (28.3)	91 (40.3)	476 (26.8)	<.001	15.4
Pneumonia	251 (12.5)	23 (10.2)	228 (12.8)	NS	24.0
Arthritis	235 (11.7)	27 (11.9)	208 (11.7)	NS	2.6
Necrotizing fasciitis	143 (7.1)	3 (1.3)	140 (7.9)	<.001	20.4
STSS	120 (6.0)	6 (2.7)	114 (6.4)	.02	44.5
Abscess	114 (5.7)	11 (4.9)	103 (5.8)	NS	3.5
Abdominal/peritoneal infection	66 (3.3)	4 (1.8)	62 (3.5)	NS	9.1
Osteomyelitis	64 (3.2)	19 (8.4)	45 (2.5)	<.001	3.1
Pregnancy-related infection	36 (1.8)	NA	36 (2.0)	NA	5.6
Endocarditis/pericarditis	29 (1.4)	0 (0)	29 (1.6)	.05	17.9
Meningitis/CNS infection	17 (0.8)	6 (2.7)	11 (0.6)	.002	37.5
Genital (not pregnancy-related) infection	3 (0.1)	0 (0)	3 (0.2)	NS	0
Other[c]	39 (1.9)	13 (5.8)	26 (1.5)	<.001	2.7

NOTE. NA, not applicable; NS, not statistically significant; STSS, streptococcal toxic shock syndrome.

[a] Data for case patients could be categorized under >1 syndrome, except for case patients identified as having bacteremia without a source.

[b] Comparison by age category of the proportion of group A *Streptococcus* disease attributable to a particular syndrome.

[c] Includes central venous catheter infection (1), endophthalmitis (1), epiglottitis (6), parotid gland infection (1), Ludwig angina (1), otitis media (17), urologic infection (10), and unknown (2).

there are 9600–9700 cases of invasive GAS disease and 1100–1300 resulting deaths, or ~3–4 times the number of cases of meningococcal disease and resulting deaths. The burden of invasive GAS disease is concentrated at the extremes of age, with the highest incidence of both disease and death in the elderly population, whereas the incidence of meningococcal disease and associated death is concentrated among younger people.

We found that the distribution of GAS *emm* types varied by geographic region and by year. GAS strains with newly characterized *emm* types are a significant cause of disease. These strains are more likely to be those that previously were characterized as nontypeable when available rabbit antisera were used than to be strains that had newly emerged [39]. Isolates with newly characterized *emm* sequence types were most common at the West Coast surveillance sites. The reason for this is not known, but it may reflect introduction from other countries. *emm* typing of strains from countries in Asia and Latin America indicates that the proportion of strains of newly characterized *emm* types is significantly greater than that among isolates collected in the United States [42–44]. The present study also shows that *emm* types are important predictors of clinical syndrome and mortality.

Current strategies for preventing morbidity and mortality resulting from invasive GAS infection are limited. The treatment of STSS with intravenous immunoglobulin and of NF with clindamycin and surgical intervention has been associated with lower mortality in observational studies [1, 45, 46]. Some cases of invasive GAS disease may be prevented through the increased use of varicella vaccine in children [1, 47], chemoprophylaxis of selected contacts of patients with invasive infection [1], improved infection control [1], and prompt investigation of outbreaks in hospitals and nursing homes [48, 49]. Prevention through vaccination against GAS could have a much greater impact than these interventions. Currently, several candidate GAS vaccines are being developed, and some are entering clinical trials. These include targets such as C5a peptidase [50], M type–specific protein [36], M-conserved protein [51, 52], and GAS toxins (streptococcal pyrogenic exotoxins A, B, and C) [53–56].

One possible limitation of strategies that use M type–specific targets is the need for a multivalent vaccine similar to that used against pneumococcal infection. Population-based studies outside North America that could be used to estimate the coverage of an *emm* type–specific GAS vaccine against invasive disease are limited [57]. Reports in the United States have shown that the most common types among patients with uncomplicated pharyngitis were 1, 2, 3, 4, 12, and 28, whereas types 3 and 18 have been associated with rheumatic fever [28, 58]. Studies from developing countries have found a greater diversity of *emm* types than is found in the United States, with many isolates being M-nontypeable when available antisera are used [42,

Table 4. Results of multivariable analysis of factors associated with death due to invasive group A *Streptococcus* disease for cases reported from 1 July 1995 through 31 December 1999.

Variable	Rate ratio (95% CI)
Race	
Other than black	Reference
Black	0.91 (0.61–1.35)
Age, years	
<18	Reference
18–49	2.62 (1.29–5.34)
50–64	3.51 (1.69–7.31)
⩾65	5.24 (2.62–10.48)
Syndrome	
Other than pneumonia, meningitis, and STSS	Reference
Pneumonia	2.20 (1.56–3.10)
Meningitis	4.96 (2.00–12.29)
STSS	3.77 (2.67–5.32)
emm type	
Not *emm1* or *emm3*	Reference
emm1	1.50 (1.11–2.04)
emm3	1.53 (1.00–2.36)

NOTE. STSS, streptococcal toxic shock syndrome.

59]. *emm* typing has now been performed on a substantial number of these strains from developing countries, and this has confirmed that a large number of types are being newly recognized (CDC, unpublished data). Country- or region-specific surveillance data would be required to determine which types are appropriate for inclusion in a serotype-specific vaccine. Multivalent type-specific GAS vaccines based on *emm* sequence types might need to be adapted to changes in prevalence if the relative importance of various *emm* types proves to be highly dynamic.

The findings of the present study are limited in some respects. The incidence rates of STSS and NF disease are minimum estimates. The results of the CDC Active Bacterial Core Surveillance routine procedures for syndrome determination were compared with those of more detailed data-collection procedures used on the same cases in selected surveillance areas. When the more detailed form is used as the standard, the routine case-report form procedures categorized only 50% of STSS cases and 40% of NF cases correctly (CDC, unpublished data). The information collected on varicella infection preceding the onset of GAS disease was not uniformly collected and likely represents an underestimation of the proportion of subjects with this underlying condition. Finally, the characterization of the strains collected during the course of this surveillance does not include data on toxin production or other potential vaccine targets. These strains, however, could be evaluated for such properties.

Ongoing studies of trends in invasive and noninvasive GAS disease incidence, clinical manifestations, and *emm* type distribution are warranted to monitor trends in disease incidence, guide public health prevention activities, and inform new strategies for disease control. Data on invasive GAS disease epidemiology are not paralleled by data of equivalent quality on strains that cause pharyngitis or noninvasive cutaneous infections, even though those disease entities result in a significant disease burden. The collection of such data should be considered a priority, along with ongoing surveillance for invasive GAS disease, to address the broad range of public health issues of GAS disease [58].

Although the reemergence of severe invasive GAS disease in the mid-1980s attracted substantial concern, we found no evidence for an increase in the absolute incidence of disease since that time. However, GAS causes a substantial burden of endemic disease, which is manifested in large part by syndromes associated with severe morbidity and high mortality. The reporting of invasive GAS disease through population-based surveillance provides a basis for tracking trends in disease incidence rates, evaluating strains that cause disease, targeting vaccine development efforts, and addressing other means of controlling disease. The control of invasive GAS disease requires a long-term commitment to prevention strategies, including the evaluation of vaccines.

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