AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

Epidemiology of Invasive Group A Streptococcal Disease in Alaska, 2001 to 2013

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The Arctic Investigations Program (AIP) began surveillance for invasive group A streptococcal (GAS) infections in Alaska in 2000 as part of the invasive bacterial diseases population-based laboratory surveillance program. Between 2001 and 2013, there were 516 cases of GAS infection reported, for an overall annual incidence of 5.8 cases per 100,000 persons with 56 deaths (case fatality rate, 10.7%). Of the 516 confirmed cases of invasive GAS infection, 422 (82%) had isolates available for laboratory analysis. All isolates were susceptible to penicillin, cefotaxime, and levofloxacin. Resistance to tetracycline, erythromycin, and clindamycin was seen in 11% ($n = 8$), 5.8% ($n = 20$), and 1.2% ($n = 4$) of the isolates, respectively. A total of 51 *emm* types were identified, of which *emm*1 (11.1%) was the most prevalent, followed by *emm*82 (8.8%), *emm*49 (7.8%), *emm*12 and *emm*3 (6.6% each), *emm*89 (6.2%), *emm*108 (5.5%), *emm*28 (4.7%), *emm*92 (4%), and *emm*41 (3.8%). The five most common *emm* types accounted for 41% of isolates. The *emm* types in the proposed 26-valent and 30-valent vaccines accounted for 56% and 78% of all cases, respectively. GAS remains an important cause of invasive bacterial disease in Alaska. Continued surveillance of GAS infections will help improve understanding of the epidemiology of invasive disease, with an impact on disease control, notification of outbreaks, and vaccine development.

Streptococcus pyogenes (group A streptococci [GAS]) is an exclusively human pathogen that is usually transmitted through contact with respiratory secretions from an infected person. GAS is most commonly associated with pharyngitis and skin infections but can also cause more serious invasive infections, including puerperal sepsis, bacteremia, pneumonia, meningitis, necrotizing fasciitis (NF), and streptococcal toxic shock syndrome (STSS) (1). It can also lead to serious nonsuppurative sequelae, such as acute rheumatic fever and rheumatic heart disease, especially in developing countries (1–3). Since the mid-1980s, a surge in the incidence and severity of GAS infections has been documented worldwide, resulting in significant morbidity and mortality (4–8). In the United States from 2000 to 2005, the annual average incidence of invasive GAS disease was 3.5 cases per 100,000 persons, with 735 deaths (case fatality rate, 13.7%) (9). Persons ≥65 years of age had the highest incidence (9.4 cases per 100,000 persons), followed by children <1 year of age (5.3 cases per 100,000 persons). The case fatality rate (22.8%) was also highest among the elderly.

Strain characterization of GAS was traditionally based on serological identification of the M protein, which is a major surface protein and an important GAS virulence factor. Classical serologic M typing in many laboratories has been replaced by *emm* typing, which in almost all cases predicts the classical M serotype (10, 11). To date, >200 different *emm* types have been reported. In most countries, *emm* types 1, 3, 12, and 28 have traditionally been associated with invasive GAS disease (9, 12–22).

Clinical management of invasive GAS infections centers on accurate diagnosis early in the course of disease and timely, appropriate use of antibiotics. Few effective prevention strategies exist. Efforts at disease prevention have been focused on vaccine development. However, development of a GAS vaccine has been challenging because of the vast number of *emm* types and because of concerns of possible induction of antibodies that cross-react with epitopes in the GAS M protein and human brain, joint, and cardiac tissues (23–25). Molecular techniques have allowed the development of multivalent M protein-based vaccines that contain protective epitopes and exclude potentially harmful tissue cross-reactive epitopes (25–28). A 26-valent vaccine containing M peptides from serotypes of GAS representing the vast majority of infections in the United States was reported as safe and immunogenic in adult volunteers (29). More recently, Dale et al. constructed a 30-valent vaccine composed of M peptides representing the majority of infections in the United States and Europe (30). In animal studies, this vaccine evoked bactericidal antibodies against all of the vaccine serotypes. This vaccine was also found to elicit significant bactericidal activity against a number of laboratory strains of GAS that were nonvaccine serotypes, suggesting increased efficacy beyond the serotypes in the vaccine (31). With this progress, baseline data on the burden of disease are critical in order to evaluate the potential utility of these candidate GAS vaccines.

The Arctic Investigations Program (AIP) began surveillance for invasive GAS infections in Alaska in 2000 as part of the invasive bacterial diseases population-based laboratory surveillance program. Here, we report the epidemiologic characteristics of invasive GAS infection in Alaska over 13 years of surveillance (2001 to 2013).

Received 6 August 2015 **Returned for modification** 29 August 2015
Accepted 20 October 2015

Accepted manuscript posted online 11 November 2015

Citation Rudolph K, Bruce MG, Bruden D, Zulz T, Reasonover A, Hurlburt D, Hennessy T. 2016. Epidemiology of invasive group A streptococcal disease in Alaska, 2001 to 2013. J Clin Microbiol 54:134–141. doi:10.1128/JCM.02122-15.

Editor: K. C. Carroll

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MATERIALS AND METHODS

Population studied. Alaska's population of 710,231 (2010 U.S. census) includes 142,000 (20%) Alaska Native (AN) and American Indian peoples, 7,100 of whom are younger than 2 years of age. Sixty-five percent of Alaska Native peoples live in rural communities, many of which are isolated villages with populations ranging from 50 to 1,000 persons. Health care for the AN population is provided through a statewide tribally operated health delivery system which includes community health practitioners at the village level, primary care providers in regional hub communities, and a referral hospital in Anchorage.

Case definition and patient characteristics. AIP conducts population-based statewide surveillance for invasive infections due to GAS and other bacterial pathogens of public health concern in Alaska. We reviewed reports of invasive GAS cases occurring from 1 January 2001 through 31 December 2013. A case of invasive GAS infection was defined as the isolation of group A *Streptococcus* from a sterile site (e.g., blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, surgical aspirate, bone, joint fluid, or internal body site) or from a wound culture accompanied by necrotizing fasciitis (NF) or streptococcal toxic shock syndrome (STSS) in a resident of Alaska. Demographic and clinical data on cases were collected by reviewing medical records and electronic documents. We did not assess sequelae such as acute rheumatic fever, rheumatic heart disease, or poststreptcoccal glomerulonephritis.

Bacterial isolates. Isolates of group A streptococci are received at the AIP laboratory in Anchorage, AK, from 23 regional hospital laboratories processing sterile site isolates in the state. GAS isolates were confirmed by β-hemolysis on sheep blood agar, Lancefield antigen grouping using a commercially available agglutination test kit (Phadebact Strep A kit), and the pyrrolidonylarylamidase test (PYR 50 test kit; Remel Inc., Lenexa, KS).

***emm* typing.** DNA extracts were prepared as follows: bacterial cells were resuspended in 300 μl 0.85% NaCl, heated at 70°C for 15 min, and centrifuged, and pellets were incubated in 50 μl 10 mM Tris and 1 mM EDTA (pH 8.0) with 2 μl hyaluronidase (30 mg/ml) and 10 μl mutanolysin (3,000 units/ml) for 30 min at 37°C, heated at 100°C for 10 min, and frozen at −30°C as modified from the protocol at http://www.cdc.gov/streplab/protocol-emm-type.html. The *emm* gene was amplified and sequenced according to the Centers for Disease Control and Prevention protocol (http://www2a.cdc.gov/ncidod/biotech/strepblast.asp).Sequence analysis was performed by a BLAST search on the Centers for Disease Control and Prevention streptococcal *emm* sequence database (http://www2a.cdc.gov/ncidod/biotech/strepblast.asp) to designate *emm* sequence type.

Antimicrobial susceptibility testing. Susceptibility testing was performed on all GAS isolates beginning in 2004 using the standard broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI), for penicillin, erythromycin, tetracycline, levofloxacin, cefotaxime, and clindamycin (32). The MIC was determined to be the lowest concentration of antibiotic that inhibited growth. The MIC results were interpreted according to the 2011 CLSI criteria which included the following breakpoints: penicillin resistance, >0.12 μg/ml; tetracycline resistance, >8.0 μg/ml; erythromycin resistance, >1.0 μg/ml; levofloxacin resistance, >8.0 μg/ml; cefotaxime resistance, >0.5 μg/ml; and clindamycin resistance, >1.0 μg/ml (32).

Statistical analysis. Incidence calculations are expressed as the number of cases per 100,000 population. Population estimates were obtained from the State of Alaska Department of Labor and Work Force Development (33). The trend in GAS rates over time was tested by use of Poisson regression. The Poisson test of GAS rates between AN persons and non-AN persons was age adjusted. We compared case fatality rates by use of the likelihood ratio chi-square test and developed a multivariate model using logistic regression. Simpson's diversity index (*D*) was used to summarize the diversity of GAS *emm* types (34). The higher the index, the greater the diversity of *emm* types. We selected Simpson's index because it gives more weight to the relatively common *emm* types and because it is less sensitive to changes in sample size (35). All *P* values are two-sided, and a value of <0.05 was considered statistically significant. When necessitated by sample size, an exact *P* value was reported.

TABLE 1 Rates of invasive group A streptococcal disease in Alaska, 2001 to 2013

Factor	Group	No. of cases	Rate (per 100,000 persons)
Yr (all ages)	2001–2013	516	5.8
	2001–2005	157	4.8
	2006–2009	144	5.3
	2010–2013	215	7.4
Age class (yr)	<2	40	14.8
	2–4	14	3.3
	5–17	32	1.8
	18–44	148	4.3
	45–64	182	7.7
	65+	100	15.7
Sex (all ages)	Male	285	6.2
	Female	231	5.4
Clinical infection[a,b]	Endocarditis	15	0.17
	Empyema	22	0.25
	Toxic shock syndrome	16	0.18
	Pneumonia	101	1.14
	Necrotizing fasciitis	41	0.46
	Septic arthritis	44	0.49
	Cellulitis	217	2.44
	Bacteremia	121	1.36
Severity measures	Hospitalizations	443	5.0
	Deaths	56	0.6
Race	Alaska Native persons	237	13.7[c]
	Non-AN persons	279	3.9[c]

[a] A case was included in the rate for a specific clinical infection if it appeared alone or in combination with other clinical infections; infections are not mutually exclusive. "Case" is defined as bacteremic only if no other infection was present.
[b] When cases are placed in only one infection, prioritized according to their display in table (top to bottom), the rates are as follows: endocarditis, 0.17; empyema, 0.25; toxic shock syndrome, 0.16; pneumonia, 0.84; necrotizing fasciitis, 0.38; septic arthritis, 0.39; cellulitis, 1.73; and bacteremia, 1.36.
[c] Age-standardized rates: 14.8 and 3.8.

RESULTS

Descriptive epidemiology, incidence rates, and clinical syndrome data. Over the 13-year study period (January 2001 through December 2013), 516 cases of invasive GAS disease were reported to AIP; 285 (55%) of the patients were male. The median age of case patients was 47.3 years. The overall incidence rate over the 13-year study period was 5.8 cases per 100,000 persons (Table 1). The rate during the period 2010 to 2013 of 7.4 cases per 100,000 persons was significantly higher ($P < 0.001$) than the rate (4.8 cases per 100,000 persons) during the first time period (2001 to 2005). Much but not all of this difference can be attributed to the increase in the number of cases in 2011 ($P = 0.02$ with 2011 data excluded), and it reflects a trend toward an increase in number of cases in 2012 and 2013 compared to previous years (Fig. 1). Rates of GAS disease were 14.8 cases per 100,000 persons among children <2 years of age and 15.7 cases per 100,000 among persons >65 years of age. Ethnicity data were

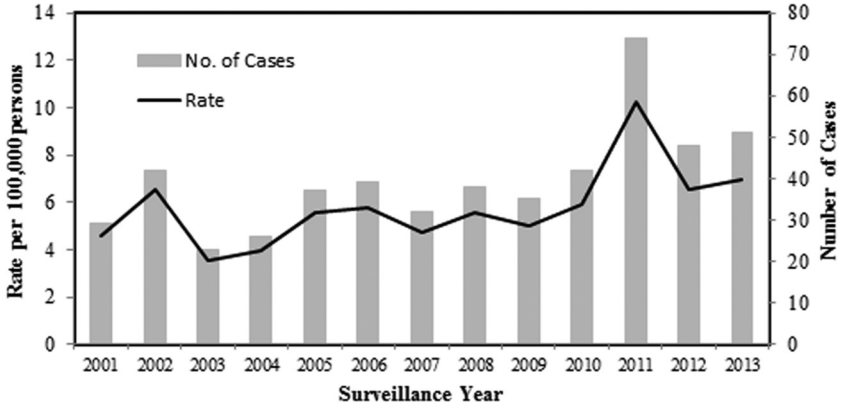

FIG 1 Incidence rates and numbers of cases of invasive group A streptococcal disease by year in Alaska, 2001 to 2013.

available for all cases; 237 (46%) occurred in AN persons (Table 1). Rates of invasive GAS disease among AN persons compared to non-AN persons were 13.7 versus 3.9 cases per 100,000 persons ($P < 0.0001$), respectively. Rates of disease among AN children <2 years of age compared to non-AN children of the same age were 39.9 versus 4.2 cases per 100,000 persons ($P < 0.0001$), respectively. Cases occurred in all regions of the state.

The most common clinical manifestations were cellulitis

TABLE 2 Risk factors for death among cases of invasive group A streptococcal disease in Alaska, 2001 to 2013

Risk factor	Group	% case fatality (ratio)	Rate ratio[a]	*P* value
Period	2001–2005	10.2 (16/157)	Ref	0.89
	2006–2009	10.5 (15/143)	1.0	
	2010–2013	11.6 (25/215)	1.1	
Sex	Female	11.7 (27/231)	1.1	0.59
	Male	10.2 (29/284)	Ref	
Age	≤64 years	8.7 (36/415)	Ref	0.001[b]
	65+ years	20.0 (20/100)	2.3	
Ethnicity	Alaska Native	8.9 (21/237)	0.7	0.18
	Non-Alaska Native	12.6 (35/278)	Ref	
emm type	1, 3, and 12	24.5 (25/102)	3.4	<0.0001[b]
	All others	7.2 (23/319)	Ref	
Endocarditis	Yes	35.7 (5/14)	2.5	0.01
	No	10.2 (51/501)	Ref	
Empyema	Yes	4.6 (1/22)	0.4	0.49
	No	11.2 (55/493)	Ref	
Toxic shock syndrome	Yes	12.5 (2/16)	1.2	0.70
	No	10.8 (54/499)	Ref	
Pneumonia	Yes	14.9 (15/101)	1.5	0.15
	No	9.9 (41/413)	Ref	
Necrotizing fasciitis	Yes	10.0 (4/40)	0.9	1.00
	No	11.0 (52/475)	Ref	
Septic arthritis	Yes	4.6 (2/44)	0.4	0.21
	No	11.5 (54/471)	Ref	
Cellulitis	Yes	6.0 (13/217)	0.4	0.002[b]
	No	14.4 (43/298)	Ref	

[a] Ref, reference.
[b] All remained significant in a multivariate logistic regression: age class ($P = 0.007$); *emm* type 1, 3, or 12 ($P < 0.0001$); and cellulitis ($P = 0.007$).

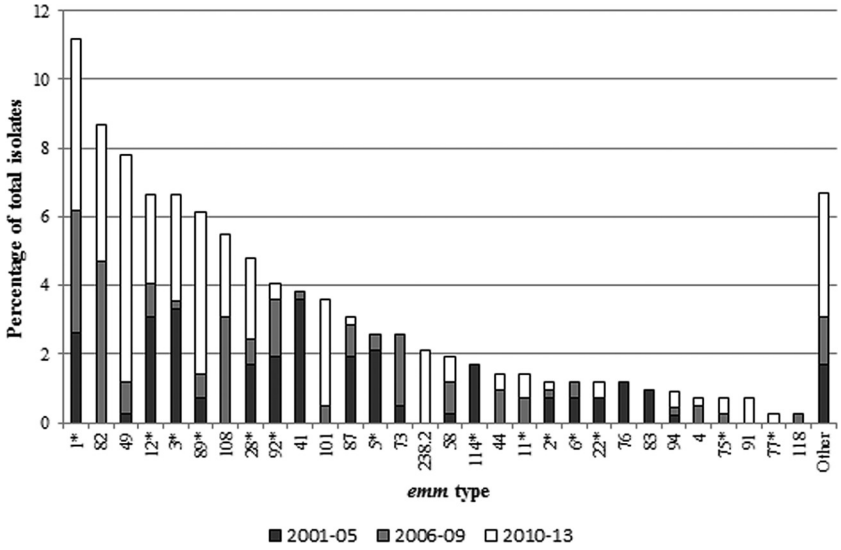

FIG 2 Distribution of *emm* types among invasive group A streptococcal isolates in Alaska by time period, 2001 to 2006, 2006 to 2009, and 2010 to 2013. Asterisks indicate *emm* types present in both the 26-valent and 30-valent vaccines. *emm* types present in the 30-valent but not in the 26-valent vaccine include types 82, 49, 87, 73, 58, 44, 83, 4, and 118. *emm* types contained in the 26-valent but not in the 30-valent include types 76, 94, and 101. *emm* types that are not included in either vaccine are types 108, 41, and 1-2.3.

(42%, $n = 217$), bacteremia (23%, $n = 121$), and pneumonia (19.6%, $n = 101$). Patients with NF and STSS accounted for 8% ($n = 41$) and 3% ($n = 16$) of cases, respectively (Table 1). Eighty-six percent (443/516) of patients were hospitalized. The median length of hospitalization was 8.0 days for all cases; 15.0 for cases of necrotizing fasciitis and 16.0 days for cases of TSS. Among the 516 case patients for whom outcome data were reported, 56 died (case fatality rate of 10.7%); four deaths were among cases with NF, and two deaths occurred in individuals diagnosed with STSS.

Risk factors for death. Risk for death increased with age ($P = 0.001$) and was highest among those ≥65 years of age (20%, $n = 20$) (Table 2). We did not find any difference in risk of death according to clinical presentation, with the exception that patients diagnosed with cellulitis were less likely to die than those without this diagnosis ($P = 0.002$). Risk for death did vary according to the *emm* type responsible for the infection. The highest risk was associated with *emm* types 1, 3, and 12, and the difference was statistically significant ($P < 0.0001$).

***emm* sequence types.** Of the 516 cases included in our study, isolates from 422 (82%) were available for evaluation. Among these 422 isolates, 51 different *emm* types were identified. The 10 most common *emm* types accounted for 65% (275/422) of isolates and included types 1, 82, 49, 12, 3, 89, 108, 28, 92, and 41 (Fig. 2). The distribution of *emm* types varied significantly over time (Table 3). The most common *emm* types seen during surveillance years 2001 to 2005 were types 41 (12%, $n = 15$), 3 (12%, $n = 12$), and 12 (11%, $n = 13$). During surveillance years 2006 to 2009, the most common *emm* types were 82 (18%, $n = 20$), 1 (13%, $n = 15$), and 108 (12%, $n = 13$). *emm* types 49 (15%, $n = 28$), 1 (11%, $n = 21$), and 89 (11%, $n = 20$) were the most common types found during surveillance years 2010 to 2013. The significant difference in *emm* types ($P < 0.0001$) between surveillance periods was accounted for by increases in *emm* types 49, 82, 89, and 108 and decreases in *emm* types 3, 12, and 41 (Fig. 2). The significant difference in *emm* types ($P < 0.0001$) by race/ethnicity was accounted for by a higher prevalence of *emm* types 49, 82, 87, 92, and 101 in AN persons and a higher prevalence of *emm* types 1, 3, 12, 28, and 89 in non-AN persons. The distribution of *emm* types did not significantly differ on the basis of sex, age (<45 years versus ≥45 years), residence (urban versus rural), or clinical presentation (cellulitis versus other).

With the possibility of two GAS vaccines coming onto the market, we evaluated the proportion of our invasive GAS cases that

TABLE 3 Comparison of *emm* type distribution among invasive group A streptococcal isolates in Alaska between 2001–2005, 2006–2009, and 2010–2013

Descriptor	2001–2005 ($n = 121$)	2006–2009 ($n = 113$)	2010–2013 ($n = 188$)
No. of *emm* types	22	28	36
Most common *emm* type (%)	41 (12)	82 (18)	49 (15)
	3 (12)	1 (13)	1 (11)
	12 (11)	108 (12)	89 (11)
% of cases (top 5 *emm* types)	51 (62/121)	57 (64/113)	53 (99/188)
% of cases (top 10 *emm* types)	80 (97/121)	74 (84/113)	80 (150/188)
Simpson's diversity index	0.92	0.90	0.93
% covered by 26-valent vaccine	72.7 (88/121)	39.8 (45/113)	55.3 (104/188)
% covered by 30-valent vaccine	80 (97/121)	79.6 (90/113)	75.5 (142/188)
Most common *emm* type(s) not in either vaccine	41	108, 9	108, 1-2.3, 91

TABLE 4 Distribution of *emm* types among antimicrobial resistant invasive group A streptococcal isolates in Alaska by time period[a]

Time period	No. of isolates	Tet^r		Ery^r		Tet^r Ery^r		Ery^r Cm^r		Tet^r Ery^r Cm^r	
		No. of isolates	*emm* type(s) (no. of isolates)	No. of isolates	*emm* type(s) (no. of isolates)	No. of isolates	*emm* type(s) (no. of isolates)	No. of isolates	*emm* type (no. of isolates)	No. of isolates	*emm* types (no. of isolates)
2004–2005	48	9	41, 87 (8)	0	NA	1	58	1	92	0	NA
2006–2009	112	16	1, 41, 49 (4), 87 (4), 108 (6)	5	92	5	58 (4), 94	0	NA	0	NA
2010–2013	183	2	44, stG6.0	3	3, 75 (2)	2	58	0	NA	3	11 (2), 94

[a] Tet, tetracycline; Ery, erythromycin; Cm, clindamycin; NA, not applicable.

were preventable with use of these vaccines (Table 3; Fig. 2). During the early surveillance period (2001 to 2005), the 26-valent vaccine covered 73% (88/121) of cases, followed by 40% (45/113) of cases during surveillance years 2006 to 2009 and 55% (104/188) of cases during 2010 to 2013. The 30-valent vaccine would have covered 80% (97/121), 77% (90/113), and 74% (142/188) of cases in surveillance years 2001 to 2005, 2006 to 2009, and 2010 to 2013, respectively. Across the 13-year surveillance period, 56% (237/422) and 76% (321/422) of the isolates were *emm* types included in the 26-valent and 30-valent vaccines, respectively. The proportion of disease accounted for by *emm* types in the 26-valent vaccine was higher among adults ≥65 years of age (59%, $n = 59$) than children <5 years of age (50%, $n = 27$). Coverage with the 30-valent vaccine was similar (79% [$n = 79$] versus 84% [$n = 45$]). When broken down by clinical syndrome, 62% (21/34) of NF cases, 67% (8/12) of STSS cases, and 73% (35/48) of deaths were potentially preventable by the 26-valent vaccine. The proportions of NF and STSS cases potentially preventable by the 30-valent vaccine were 68% (23/34) and 75% (9/12), respectively, and at least 85% (41/48) of deaths were preventable by this vaccine. A diversity of *emm* types was detected in isolates from patients with the most severe forms of infection (NF and SSTS). Among the 34 cases of NF, 20 different *emm* types were observed; the most common types included 1 ($n = 5$), 12 ($n = 4$), and 89 ($n = 3$). Eight different *emm* types were observed among the 12 cases of STSS; the most common types included 1 ($n = 4$) and 3 ($n = 2$).

Antimicrobial susceptibility. Of the 343 isolates tested, all were susceptible to penicillin, cefotaxime, and levofloxacin. Resistance to tetracycline, erythromycin, and clindamycin was seen in 11% ($n = 38$), 5.8% ($n = 20$), and 1.2% ($n = 4$) of the isolates, respectively (Table 4). The proportion of isolates resistant only to tetracycline varied over time. From 2004 to 2008, 20% (25/127) of isolates were resistant to tetracycline, compared to <1% (2/216) during surveillance years 2009 to 2013 ($P < 0.001$). The majority (81%) of the isolates resistant only to tetracycline during the early surveillance years were *emm* types 87 ($n = 12$), 108 ($n = 6$), and 49 ($n = 4$).

The majority (65%) of isolates resistant only to erythromycin were *emm* type 92 ($n = 5$) and 75 ($n = 2$). Nine isolates (2.6%) were resistant to both tetracycline and erythromycin and were represented by *emm* types 58 ($n = 7$) and 94 ($n = 2$). All *emm* types associated with tetracycline and erythromycin resistance in our study, except *emm*108, are contained in both the 26-valent and 30-valent vaccines.

DISCUSSION

Here, we report a comprehensive description of the epidemiology of group A streptococcal disease in the state of Alaska from 2001 to 2013, including information on *emm* type prevalence. With the reemergence of invasive GAS disease in the 1980s, there have been numerous reports published describing the burden of GAS disease in industrialized countries (7, 9, 13, 17–20, 36). In these reports, invasive GAS disease rates ranged from 1.5 to 5.8 cases/100,000 persons. In the United States, O'Loughlin et al. (9) reported a mean incidence of 3.5 cases/100,000 persons from 2000 to 2004 among the CDC's Active Bacterial Disease Surveillance network, which is within the range reported worldwide. However, a recent study by Stockmann et al. reported a mean annual incidence rate of 6.3 cases/100,000 persons among Utah residents, with the rate increasing from 3.5 cases/100,000 persons in 2002 to 9.8 cases/100,000 persons in 2010 (37). The overall annual incidence of invasive GAS disease in Alaska is slightly higher (5.8/100,000 population) than reported from CDC's Active Bacterial Disease Surveillance network (3.7/100,000; 2001 to 2013; http://www.cdc.gov/abcs/reports-findings/surv-reports.html). When we compared the incidence among Alaska Native persons (13.7/100,000) to that in non-AN persons (3.9/100,000), the rate was much higher among AN persons and similar to what has been reported for developing countries such as Fiji and for indigenous populations in Australia and New Zealand (38–40). In our study, the highest burden of disease was found among children <2 years of age (14.8 cases/100,000 persons) and adults >65 years of age (15.7 cases/100,000 persons). These rates are higher than what was reported for the general U.S. population from 2001 to 2013 (4.6 cases/100,000 in children <2 years old and 9.7 cases/100,000 in adults ≥65 years old; http://www.cdc.gov/abcs/reports-findings/surv-reports.html) and is most likely due to the higher rates of disease among Alaska Native persons.

The most prevalent clinical manifestation was cellulitis, comprising 42% of all invasive cases, which is similar to what has been reported in several countries in Europe and the United Kingdom (18, 41). Other studies from the United States have reported that the clinical syndromes associated with invasive GAS disease vary from year to year (8, 9, 37). The overall case fatality rate reported in our study was 10.7% which is similar to what has been reported by others. The highest case fatality rate in our study was associated with persons diagnosed with endocarditis (35.7%).

In this study, the five most common *emm* types were types 1, 3, 12, 49, and 82. Of these, *emm* types 1, 3, and 12 have been reported to be among the most prevalent types causing invasive disease worldwide (41). However, there are significant differences in *emm* type distribution by region and country, with a much greater diversity of strains in low-income settings. Using Simpson's index of diversity, which reflects the probability that two isolates selected at

random from the same population will be of different *emm* types, we calculated a diversity index of 0.92 among our isolates. This was similar to what has been reported for other high-income settings but not as high as what has been reported for regions such as Africa and the Pacific, where the diversity index ranged from 0.97 to 0.98 (41).

We found considerable variation in the distribution of *emm* types between the three time periods analyzed. Variation in the relative prevalence of predominant *emm* types over time is not unique to our study, as others have also found significant variability (12–14, 18, 20, 36, 42). Such variability can potentially limit the usefulness of vaccines based on the M protein. We did note, however, that some *emm* types (types 1, 12, 28, 58, 89, and 92) in our study were seen in all or most surveillance years, while other *emm* types emerged for a limited time (types 5, 41, 73, 76, 83, and 114) and then declined. Notably, *emm* type 49 cases seemed to have higher mortality (4 deaths in 18 cases versus 4 deaths in 41 cases for non-*emm*49 cases); however, this did not reach statistical significance ($P = 0.095$). In other studies, *emm* type 49 strains have been associated with severe invasive infections and evasion of the host neutrophilic defenses (43, 44).

We investigated whether certain *emm* types are associated with particular clinical syndromes or mortality and found that mortality was significantly associated with *emm* types 1, 3, and 12, but we did not observe an association between *emm* type and severe disease (NF and STSS). A few studies have shown a positive correlation between *emm* type and disease severity (8, 14, 15, 17, 41). Among the 34 cases of NF in our study, 20 different *emm* types were observed, including five cases with *emm*1. Among the 12 cases of STSS, eight different *emm* types were found, including four cases with *emm*1. The relative importance of any individual *emm* type in disease severity is likely the result of a combination of multiple factors, such as the relative frequency of *emm* types circulating within a community, the degree of individual and community-level immunity to the circulating strains, and the invasiveness of these strains.

While there has been an apparent reemergence of invasive GAS disease in the last few decades, strategies for preventing morbidity and mortality are still limited. In this study, *emm* types contained in the proposed 26-valent vaccine accounted for 56% of all isolates, while the proposed 30-valent vaccine accounted for 78% of all isolates. However, there was considerable variability in the proportion of *emm* types included in both of these vaccines by year. Knowing how a vaccine would match the epidemiology of GAS *emm* types is useful for planning purposes. However, the effectiveness of a GAS vaccine in Alaska would also depend greatly on the specific recommendations for age and risk groups, vaccine uptake, and efficacy of the vaccine against invasive disease.

Recently, a functional classification based on 48 *emm* clusters containing closely related M proteins that share binding and structural properties was proposed (45). In this classification system, M proteins included in the same *emm* cluster demonstrate, by definition, an average pairwise identity of >70% and share similar binding properties, and therefore they potentially provide immunologic cross-protection. While the authors of that study do not suggest replacing *emm* typing with *emm* cluster typing, they suggest that this new classification system will help facilitate the design of studies to investigate GAS molecular epidemiology and can support vaccine design and evaluation. Using this classification system, we observed that the 51 *emm* types identified in our study, belonged to 16 *emm* clusters (data not shown). Seven *emm* clusters were responsible for the majority (90%) of cases.

All isolates in this study were susceptible to penicillin, cefotaxime, and levofloxacin, whereas resistance was observed for tetracycline, erythromycin, and clindamycin. The percentage of overall tetracycline resistance among GAS isolates in this study was 13.6%, which is comparable to what has been reported in other studies (7, 12, 15, 18). However, tetracycline resistance was significantly higher during the early surveillance years (23.6%; 2004 to 2008) than in the later surveillance years (3.7%; 2009 to 2013) ($P < 0.001$). This decline was the result of a decrease in the number of *emm*87 isolates in the later surveillance years. The proportion of GAS isolates that were resistant to erythromycin (5.8%) was comparable to what has been reported in other studies (15, 17, 42, 46). The majority (65%) of erythromycin-resistant isolates belonged to *emm* types 58 and 92. Other studies have found erythromycin resistance associated with *emm* types 4, 11, and 28 (15, 16, 18, 21, 42). Resistance to both tetracycline and erythromycin was associated with *emm* types 58 and 94, of which *emm*58 was more common (78%).

In conclusion, this is the first report on the epidemiology of invasive GAS disease and *emm* type distribution in Alaska. The overall annual incidence of GAS in Alaska is slightly higher than reported in other populations, which is most likely driven by higher rates of disease among the AN population. As reported elsewhere, we found significant variation in *emm* type distribution, which warrants continued surveillance to assess the potential utility of proposed GAS vaccines.

ACKNOWLEDGMENTS

We thank the clinicians and microbiology laboratory personnel of the hospitals participating in statewide surveillance for invasive group A streptococcal disease in Alaska. We also thank the entire staff at the Arctic Investigations Program for their contributions to this study.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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