

Surveillance of Invasive Bacterial Disease in Alaska, 2012

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Alaska Statewide Invasive Bacterial Disease

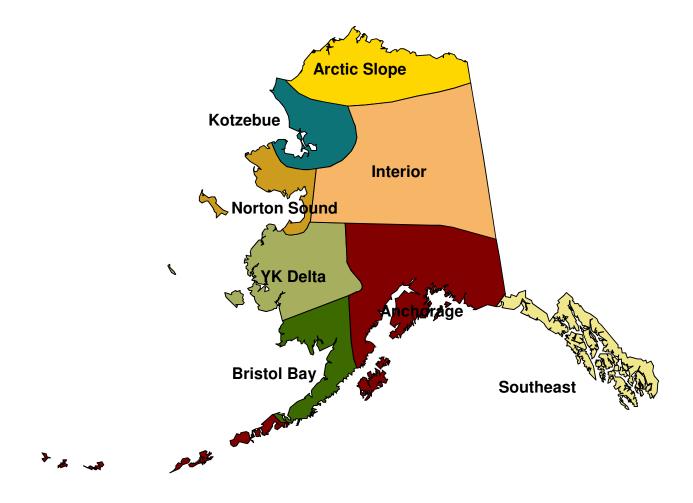
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Summary

The Centers for Disease Control and Prevention's Arctic Investigations Program (AIP) in Anchorage, Alaska, maintains a statewide surveillance system for invasive diseases caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, and groups A and B streptococci. Laboratories throughout the state are requested to send to AIP any isolates of these organisms recovered from a blood culture, CSF, or other normally sterile site in an Alaska resident. Isolate identification is confirmed and, when appropriate, serotyped and tested for antimicrobial susceptibility. The objectives of this system are to provide information on disease rates within the state, monitor the emergence of antimicrobial resistance, and to monitor the effectiveness of implemented vaccine programs, such as the 23-valent pneumococcal polysaccharide vaccine, the pneumococcal conjugate vaccine and *Haemophilus influenzae* type b vaccines.





In 2012, the total numbers of cases of invasive disease caused by these organisms reported to AIP were 130 *S. pneumoniae*, 15 *H. influenzae*, 2 *N. meningitidis*, 48 group A streptococci (GAS) and 33 group B streptococci (GBS). Alaska Native people had higher rates of disease overall than non-Native people for

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all surveillance organisms. Rates of invasive pneumococcal disease were highest in the YK Delta and Kotzebue regions. Rates for each organism by region are presented in the following table.

Region	S. <i>pneumoniae</i> n (rate*)	<i>H. influenzae</i> n (rate*)	<i>N. meningitidis</i> n (rate*)	GAS n (rate*)	GBS n (rate*)
Anchorage	58 (12)	6 (1.2)	1 (0.2)	28 (5.8)	20 (4.1)
Arctic Slope	4 (45.9)	0 (0)	0 (0)	0 (0)	1 (11.5)
Bristol Bay	2 (27.4)	1 (13.7)	0 (0)	1 (13.7)	0 (0)
Interior	21 (18.4)	1 (0.9)	1 (0.9)	7 (6.1)	5 (4.4)
Kotzebue	5 (59.7)	0 (0)	0 (0)	3 (35.8)	1 (11.9)
Norton Sound	3 (30.4)	0 (0)	0 (0)	1 (10.1)	0 (0)
Southeast	12 (16.1)	2 (2.7)	0 (0)	3 (4)	3 (4)
YK Delta	25 (98.2)	5 (19.6)	0 (0)	5 (19.6)	3 (11.8)
Total	130 (17.8)	15 (2.1)	2 (0.3)	48 (6.6)	33 (4.5)

Table 1: Surveillance Organisms Reported	d by Region – Alaska, 2012
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*Cases per 100,000 population

Introduction

AIP conducts statewide surveillance of invasive *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, and groups A and B *Streptococcus*. This program is part of a passive, laboratory-based surveillance system in which laboratories from all hospitals throughout the state are encouraged to participate. The population included in the AIP surveillance is the State of Alaska, which totaled 731,827 persons in 2012 [1]. Case detection occurs year-round as participating laboratories send isolates recovered from sterile sites to the AIP laboratory by AIP. Demographic and forms for isolate shipment and data collection are provided to each laboratory by AIP. Demographic and clinical information on the cases are collected from a review of medical records. At year-end, AIP asks that each laboratory review their records and provide information on any cases that may have been overlooked. In 2012, 23 laboratories in Alaska participated in the invasive disease surveillance system, either by sending isolates to the AIP laboratory throughout the year, conducting year-end record reviews, or both. Beginning in January, 2007, invasive *S. pneumoniae*, GAS and GBS became reportable conditions to the State of Alaska Division of Public Health (DPH). Reports of cases of disease caused by these organisms, along with cases of invasive *H. influenzae* and *N. meningitidis* which were previously reportable, are shared between AIP and DPH.

AIP defines a case of invasive *S. pneumoniae*, *H. influenzae*, *N. meningitidis*, GAS or GBS as an isolate of the bacteria from a normally sterile site, including blood, cerebrospinal fluid, pleural fluid, peritoneal fluid or joint fluid that has been taken from a resident of Alaska. In addition, for GAS, isolates are requested from deep tissue infections such as might be collected from surgical debridement of cases of necrotizing fasciitis.

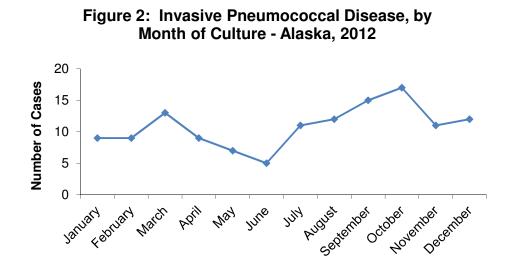
Invasive Pneumococcal Disease

Overall Incidence

A total of 123 pneumococcal isolates were received at AIP in 2012. An additional 2 cases were detected through year-end follow up with participating laboratories and 5 cases through shared surveillance with the State DPH for a total of 130 cases of invasive pneumococcal disease. The overall rate for invasive pneumococcal disease in 2012 was 17.8 cases per 100,000 persons per year. Alaska rates for 2012 were higher than the Active Bacterial Core Surveillance (ABCs) 2012 national projected rate of 10.1/100,000 [2]. ABCs is a surveillance system operated in 10 states which covers a population of up to 42 million persons.

Seasonality

Invasive *Streptococcus pneumoniae* cases were identified in each month of 2012. The largest number of cases (n=17) was reported in October.



Race

In 2012, the state population was comprised of 19.5% Alaska Native people (*Alaska Natives 142,435, non-Natives 589,392*) [1]. Of all reported *S. pneumoniae* cases in 2012, 52% occurred among Alaska Native people for a total of 68 cases; the age-adjusted rate was 52.5/100,000 persons per year. Sixty-two cases occurred among the non-Native population for an age-adjusted rate of 9.7/100,000 persons per year. The rate ratio of age-adjusted rates of *S. pneumoniae* disease for the Alaska Native population compared with the non-Native population in 2012 was 5.4.

Race	Cases n (%)	Age Adjusted Rate*	% Male	Deaths n (%)
Alaska Native	68 (52)	52.5	62%	10 (14.9)‡
Non-Native [†]	62 (48)†	9.7	63%	7 (11.3)
Total	130		62%	17 (13.1)

 Table 2: Invasive Streptococcus pneumoniae Cases by Race – Alaska, 2012

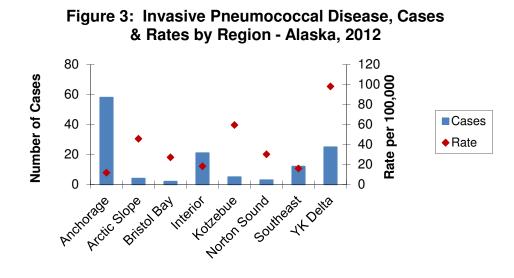
*Cases per 100,000 per percent distribution of Alaska 2010 population

†Includes 5 cases for which race was unknown

‡Outcome unknown in 1 case

Region

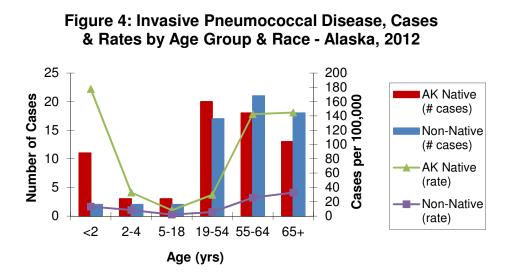
The highest percentage (45%) of invasive pneumococcal disease cases occurred in the Anchorage area in 2012. Rates of disease, however, were highest in the Kotzebue region (59.7/100,000 persons per year) and the YK Delta (98.2/100,000 persons per year).



Age

Cases occurred in all age groups in 2012 ranging from 1 month to 99.5 years with a median age of 57 years. Overall, the highest rates of disease occurred in children less than two years old.

When stratified by age and race, the highest rates of disease in 2012 occurred in Alaska Native children less than two years old (177.5/100,000 persons per year).



Since the initiation of a pneumococcal 7-valent conjugate vaccine program in 2001, overall rates of invasive disease declined dramatically in children less than 2 years of age [3]. In 2008, the rate of invasive pneumococcal disease in children less than 2 years declined to 65.6/100,000 which was the lowest rate observed in this age group since introduction of the 7-valent vaccine. Following introduction of a 13-valent conjugate vaccine in 2010, rates of disease observed in children less than 2 years old declined to 18/100,000 in 2011. In 2012, however, disease rates in this age group increased to 60.3/100,000 due to disease caused by serotypes not included in the current vaccine.

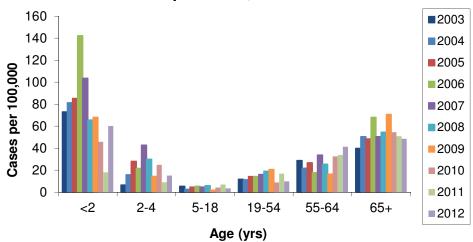


Figure 5: Invasive Pneumococcal Disease by Age Group - Alaska, 2003-2012

Although pneumococcal disease rates dropped initially in AK Native and non-Native children less than 2 years of age after introduction of the 7-valent vaccine, the rates of disease in AK Native children less than 2 years trended upward from a low of 93.6/100,000 in 2001 to 335.9/100,000 in 2006. This increase in rates was due primarily to disease caused by serotypes not contained in the pneumococcal conjugate vaccine [4,5]. In 2009, rates of disease in AK Native children less than 2 years declined to 87.1/100,000 which was the lowest rate since the introduction of the seven-valent pneumococcal vaccine. After introduction of the 13-valent vaccine in 2010, rates declined to 30.7/100,000 in 2011, however, increased to 177.5/100,000 in 2012; 10 of 11 (91%) cases were caused by non-vaccine

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serotypes. Rates of invasive disease in non-Native children less than 2 years declined during the same time period reaching 26.8/100,000 in 2005, and following an increase to 64.4/100,000 in 2007, declined in 2008 to 6.2/100,000. In 2009, the rate of disease in non-Native children less than 2 years increased to 60.3/100,000, but declined to 13/100,000 in 2012 with use of the 13-valent vaccine.

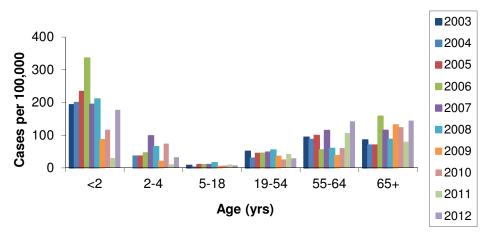
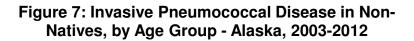
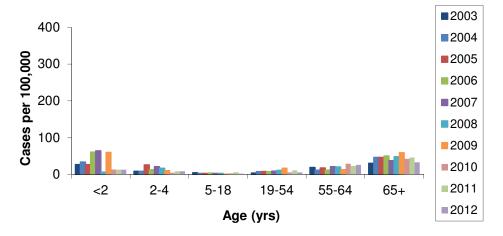


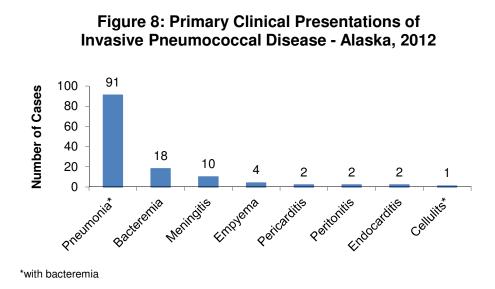
Figure 6: Invasive Pneumococcal Disease in Alaska Natives, by Age Group - Alaska, 2003-2012





Clinical Presentation

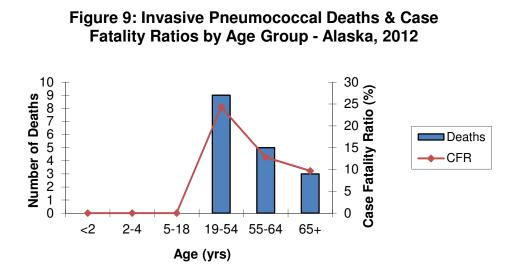
The primary clinical presentation was determined by a review of the discharge diagnoses in each patient's individual medical record associated with the invasive bacterial illness. In cases with multiple discharge diagnoses, the most serious diagnosis related to the pneumococcal infection was recorded as the primary clinical presentation. Pneumonia with bacteremia was the most common primary clinical presentation in 2012 (70%) followed by bacteremia (14%). Twenty-six cases had a secondary pneumococcal-related diagnosis in 2012 - 13 pneumonia, 3, empyema, 2 endocarditis, 1 cellulitis, 1 osteomyelitis and 6 unspecified presentations.



In 2012, blood was the most common source of a positive culture which was used to identify 120 (92%) of 130 cases. Cerebrospinal fluid was the positive site for 5 (4%) of cases; two cases were identified from pleural fluid and one each from joint and peritoneal fluid. One case was identified using PCR on pleural fluid from a person pre-treated with antibiotics.

Mortality

In 2012, the overall case fatality ratio for *S. pneumoniae* in Alaska was 13.1% (17 deaths out of 129 cases for which outcomes were known). The case fatality ratio for AK Natives was slightly higher (14.9%, 10 deaths) than non-Natives (11.3%, 7 deaths). The largest number of deaths and the highest case fatality ratio occurred in the 19-54 age category (9 deaths) 24.3%.



Serotype

Serotyping of invasive pneumococcal isolates is performed at AIP using internationally standardized methods. Serotype identification is based on the organism's polysaccharide capsule which is a principal virulence factor for pneumococci. This information provides a way to categorize organisms and to determine if the infection was due to a type that could be prevented by use of one of the available pneumococcal vaccines. Serotyping was performed on all of the *S. pneumoniae* cases for which an isolate was available.

		Alaska Native				Non	-Native		
Serotype	Total n (%)	<2	2-18	19-64	65+	<2	2-18	19-64	65+
03	12 (10)	-	1	6	1	-	-	4	-
06A	1(1)	-	1	-	-	-	-	-	-
06C	4 (3)	-	-	-	-	-	-	2	2
07C	1(1)	-	-	-	-	-	-	-	1
07F	10 (8)	-	-	2	1	-	-	5	2
08	5 (4)	-	-	4	-	-	-	1	-
09N	3 (2)	-	-	-	1	-	-	1	1
10A	3 (2)	-	-	-	1	-	-	1	1
11A	2 (2)	-	1	-	-	-	-	1	-
12F	8 (7)	2	1	3	-	-	-	2	-
15A	7 (6)	4	-	2	-	-	-	1	-
15C	1(1)	-	1	-	-	-	-	-	-
16F	2 (2)	-	-	1	1	-	-	-	-
17F	1(1)	-	-	1	-	-	-	-	-
19A	8 (7)	-	1	1	-	1	-	4	1
19F	2 (2)	1	-	-	-	-	-	-	1
20	9 (7)	-	-	5	2	-	1	1	-
21	1(1)	1	-	-	-	-	-	-	-
22A	1(1)	1	-	-	-	-	-	-	-
22F	12 (10)	-	-	2	1	1	1	4	3
23A	5 (4)	-	-	1	1	-	-	2	1
23B	2 (2)	-	-	-	-	-	-	2	-
31	6 (5)	-	-	4	-	-	-	-	2
33F	8 (7)	1	-	-	2	-	2	2	1
35B	4 (3)	1	-	1	-	-	-	-	2
35F	2 (2)	-	-	1	-	-	-	1	-
38	2 (2)	-	-	-	-	-	-	2	-
Total	122	11	6	34	11	2	4	36	18

Table 3:	Invasive	Pneumococcal	Serotype	Distribution h	v Race and Ao	e Group -	- Alaska.	2012
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In 2012, the most common pneumococcal serotypes were 22F, (12 isolates, 10%), 3 (12 isolates, 10%) and 7F (10 isolates, 8%). From 1986 through 2001, serotype 14 was the most common invasive pneumococcal serotype ranging from 7.4% to 23.5% of isolates. Following introduction in 2001 of the pneumococcal conjugate vaccine which includes serotype 14, the proportion of serotype 14 isolates dropped to 1.5% of serotyped isolates in 2006 and the last case was in 2009. Disease caused by serotypes 7F and 19A, which are not included in the 7-valent conjugate vaccine, continually increased until the introduction of the 13-valent vaccine in 2010 which does include these two serotypes. Although cases caused by 7F and 19A continue to occur, they are no longer the most common serotypes and it is anticipated that the number of cases will continue to decline with the use of the vaccine. The majority (67%) of serotype 22F cases and serotype 3 cases (42%) occurred in the Anchorage area in 2012.

Serotype	Anchorage	Arctic Slope	Bristol Bay	Interior	Kotzebue	Norton Sound	Southeast	YK Delta
03	5	2	-	3	-	-	2	-
06A	-	-	-	-	-	-	-	1
06C	2	-	-	2	-	-	-	-
07C	-	-	-	1	-	-	-	-
07F	7	-	-	1	-	-	2	-
08	1	-	-	-	-	1	-	3
09N	2	-	-	-	1	-	-	-
10A	2	-	-	-	-	1	-	-
11A	2	-	-	-	-	-	-	-
12F	-	-	-	2	-	-	-	6
15A	1	-	-	-	-	-	2	4
15C	1	-	-	-	-	-	-	-
16F	1	-	-	-	1	-	-	-
17F	-	1	-	-	-	-	-	-
19A	4	-	-	2	-	1	1	-
19F	1	-	-	-	-	-	-	1
20	3	1	-	1	1	-	1	2 1
21	-	-	-	-	-	-	-	1
22A	-	-	-	-	-	-	-	1
22F	8	-	-	1	-	-	2	1
23A	3	-	-	-	-	-	-	2
23B	-	-	-	1	-	-	1	-
31	5	-	-	-	1	-	-	-
33F	3	-	-	4	-	-	-	1
35B	2	-	-	-	-	-	1	1
35F	-	-	-	1	-	-	-	1
38	1	-	-	1	-	-	-	-
Unknown	4	-	2	1	1	-	-	-
Total	58	4	2	21	5	3	12	25

 Table 4: Invasive Pneumococcal Serotype Distribution by Region – Alaska, 2012

Vaccine Serotypes

In 2001, the pneumococcal conjugate vaccine (PCV7) was included in the Alaska childhood vaccination schedule. This vaccine provided protection against the 7 most common pneumococcal serotypes causing invasive disease among children (types 4, 6B, 9V, 14, 18C, 19F, 23F). In early 2010, a new pneumococcal conjugate vaccine (PCV13) was introduced into the Alaska childhood vaccination schedule. This vaccine provided protection against the 7 pneumococcal serotypes contained in the PCV7 vaccine plus six additional serotypes (1, 3, 5, 6A, 7F, 19A) that have caused invasive disease since the introduction of the PCV7 vaccine. The table below shows the proportion of invasive infections from 2012 that were due to serotypes found in the PCV13 vaccine. There were four cases of pneumococcal disease caused by serotypes contained in the PCV13 vaccine in children less than 5 years

of age, the age group for which the vaccine is recommended. It is anticipated that the number of cases caused by these serotypes will decrease over time.

Age (yrs)	Alaska Native (%)	Non-Native (%)	Total (%)
<2	1 (9%) of 11	1 (50%) of 2	2 (15%) of 13
2-4	2 (67%) of 3	0 (0%) of 2	2 (40%) of 5
5+	12 (25%) of 48	17 (30%) of 56	29 (28%) of 104
Total	15 (24%) of 62	18 (30%) of 60	33 (27%) of 122

 Table 5: Proportion of Invasive Isolates Contained in the PCV13 Vaccine by Age Group and Race

 - Alaska, 2012

For the year covered by this report, the 23-valent polysaccharide vaccine (Ps23V) was recommended in Alaska for all persons 65 years and older, and for persons over age 2 who are at higher risk for pneumococcal disease [5]. In 2012, for persons 65 years and older, 19 (66%) of 29 cases serotyped were potentially vaccine preventable invasive pneumococcal illnesses.

Vaccine Failures

In 2012, pneumococcal vaccine status was known for 112 (86%) of the 130 cases; 62 cases (55%) of cases with known vaccine status did receive a pneumococcal vaccine prior to illness and 50 cases (45%) had no record of a pneumococcal vaccine.

A PCV13 vaccine failure is defined as invasive pneumococcal disease caused by a serotype contained in the PCV13 vaccine in a child less than five years old who has had at least two doses of vaccine. There were three vaccine failures in 2012. All three children were less than three years old and presented with pneumonia; two of them presented with empyema. All three children were anemic. Serotypes of the cases were 19A (n=2) and 3 (n=1).

Potentially Preventable Deaths

Overall, 35% of all pneumococcal-related mortality in 2012 was potentially preventable with the use of the 23-valent polysaccharide vaccine in persons over 2 years old; 59% of deaths were due to disease caused by serotypes not contained in the 23-valent vaccine.

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Serotypes	< 2 years	2-4	5-18	19-54	55-64	65+	Total
PCV13	0	0	0	0	0	0	0
Ps23V	0	0	0	3 (33%)	2 (40%)	1 (33%)	6 (35%)
Non-Vaccine	0	0	0	5 (56%)	3 (60%)	2 (67%)	10 (59%)
Unknown	0	0	0	1 (11%)	0	0	1 (6%)
Total	0	0	0	9	5	3	17

Table 6: Potentially Vaccine Preventable Invasive Pneumococcal Deaths – Alaska, 2012

Six of the 17 deaths in 2012 from invasive *S. pneumoniae* occurred from serotypes contained within the Ps23V vaccine; one of the deaths was in an individual eligible for the vaccine. This death occurred in a vaccinated individual; time since vaccination was 2 years.

Table 7. Invasive r neumococcai Disease, S							
	Deaths	Serotype					
Serotype	n (%)	Frequency (n)					
03†*	1 (8%)	12					
06C	2 (50%)	4					
09N*	1 (33%)	3					
15A	1 (14%)	7					
16F	2 (100%)	2					
20*	2 (22%)	9					
22F*	2 (17%)	12					
23B	1 (50%)	2					
31	1 (17%)	6					
35B	1 (25%)	4					
35F	2 (100%)	2					
1.0		1					

Table 7: Invasive	e Pneumococcal Dise	ease, Serotypes of Fat	al Cases – Alaska, 2012

† Serotypes contained in the 13-valent conjugate vaccine *Serotypes contained in the 23-valent polysaccharide vaccine

Associated Risk Factors

The presence of one or more associated risk factors was reported in 85% of invasive pneumococcal cases in 2012. Cigarette smoking was the most prevalent risk factor observed in adults followed by alcohol abuse and chronic lung disease.

Medical Condition/Risk	Adult Cases (≥ 18 years)
Factor	n=102, Cases (%)
Cigarette smoking	46 (45%)
Alcohol abuse	31 (30%)
Chronic lung disease	30 (29%)
Diabetes	18 (18%)
Immunosuppressive treatment	3 (3%)
Injection drug use	1 (1%)
Asplenia	1 (1%)

Table 8: Associated Medical Risk Factors in Invasive Pneumococcal Cases – Alaska, 2012*

*More than one risk factor was identified in several cases

Antibiotic Resistance

Susceptibility testing was performed on 121 isolates received in 2012. Results of the testing are presented in the following table.

Antibiotic	Susceptible	Intermediate	Resistant	I + R	Total Tested
Penicillin	98 (81%)	0 (0%)	23 (19%)	23 (19%)	121
TMP-sulfa	99 (82%)	12 (10%)	10 (8%)	22 (18%)	121
Erythromycin	96 (79%)	0 (0%)	25 (21%)	25 (21%)	121
Ceftriaxone	111 (92%)	6 (5%)	4 (3%)	10 (8%)	121
Tetracycline	107 (88%)	0 (0%)	14 (12%)	14 (12%)	121
Chloramphenicol	121 (100%)	0 (0%)	0 (0%)	0 (0%)	121
Vancomycin	121 (100%)	0 (0%)	0 (0%)	0 (0%)	121
Levofloxacin	121 (100%)	0 (0%)	0 (0%)	0 (0%)	121
Clindamycin	108 (89%)	0 (0%)	13 (11%)	13 (11%)	121

Cut points from the Minimum Inhibitory Concentration (MIC) Interpretive Standards were used to determine if an isolate was 'susceptible', 'intermediate', or 'resistant' to the antibiotic being tested [7]. The MIC Interpretive Standards definitions of 'susceptible', 'intermediate', and 'resistant' can be found in the Appendix.

Serotypes found in the PCV7 and PCV13 vaccines are more likely to be non-susceptible to penicillin and erythromycin than non-vaccine serotypes. One potential benefit of the use of these vaccines was an anticipated decline in antibiotic resistance among circulating pneumococci. Following the initiation of the PCV7 vaccine in 2001, antibiotic resistance among invasive pneumococci dropped. During 2003, TMP-sulfa and penicillin resistance increased, however, following an increase in disease caused by serotype 19A. This serotype is included in the PCV13 vaccine; decreasing proportions of resistant isolates tested may be due to the introduction of the vaccine.

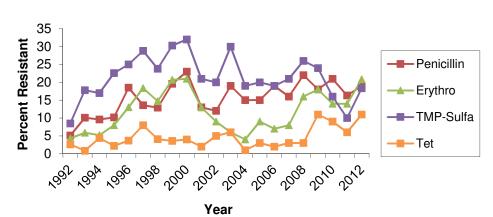


Figure 10: Trends in Antibiotic Resistance Among Invasive Pneumococcal Isolates - Alaska, 1992 - 2012

Invasive Haemophilus influenzae

Overall Incidence

In 2012, there were 15 cases of invasive *Haemophilus influenzae* in Alaska, for a statewide rate of 2/100,000 persons per year. This rate is slightly higher than the national projected rate of 1.67/100,000 persons per year [8]. There was one death caused by *H. influenzae* in 2012 for a case fatality ratio of 7%.

Seasonality

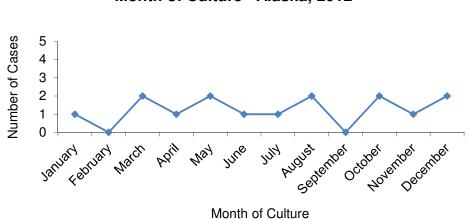


Figure 11: *Haemophilus influenzae* Disease by Month of Culture - Alaska, 2012

Cases of invasive *H. influenzae* occurred throughout 2012; however, due to the small number of cases, trends in seasonality cannot be determined.

Region

The highest rates of disease caused by invasive *H. influenzae* cases in 2012 were in YK Delta, 19.6/100,000 (5 cases), and Bristol Bay, 13.7/100,000 (1 case). Although a large number of cases occurred in the Anchorage area (6 cases), the rate was much lower (1.2/100,000).

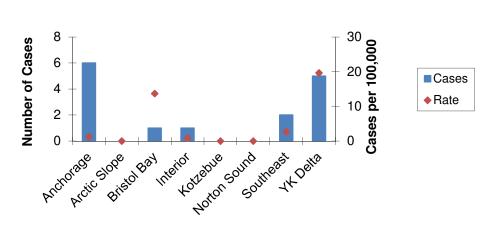


Figure 12: Invasive *Haemophilus influenzae*, Cases & Rates by Region - Alaska, 2012

Race

Table 10: Invasive Haemophilus influenzae Cases by Race – Alaska, 2012

Daga	Cases	Age Adjusted	Ø Mala	Deaths
Race	n (%)	Rate*	% Male	n (%)
Alaska Native	10 (67%)	6.8	80%	1 (10%)
Non-Native	5† (33%)	0.8	20%	0 (0%)
Total	15		60%	1 (7%)

*Cases per 100,000 per percent distribution of Alaska 2010 population

†Includes two cases for which race is unknown

In 2012, 67% of the cases occurred in Alaska Natives. Age-adjusted rates were calculated for Alaska Natives and non-Natives. The age-adjusted rate ratio of *H. influenzae* disease for the Alaska Native population compared with the non-Native population in 2012 was 8.5.

Age

H. influenzae cases ranged in age from four months to 79 years of age in 2012 (median 51 years). Overall, the highest rates of disease occurred in children less than 2 years old.

Rates of disease in Alaska Native versus non-Native populations by age group were variable; overall numbers of cases and rates by race and age group are presented in Figure 14. The highest rates of disease occurred in Alaska Native children less than two years of age, 64.6/100,000 persons per year and Alaska Native adults 55-64 years, 15.8/100,000 persons per year.

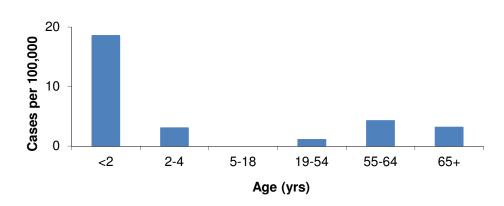
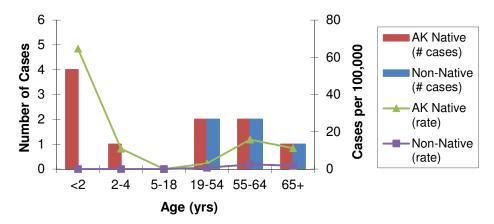


Figure 13: Invasive *Haemophilus influenzae* by Age Group - Alaska, 2012





Clinical Presentation

The primary clinical presentation was determined by a review of the discharge diagnoses in each patient's individual medical record associated with the invasive bacterial illness. For cases with more than one diagnosis, the most serious *H. influenzae*-related diagnosis was recorded as the primary clinical presentation. In 2012, pneumonia with bacteremia was the most common presentation (60% of cases).

Thirteen (87%) of *H. influenzae* isolates were from blood samples in 2012, one was from cerebral spinal fluid and one from an unidentified other sterile site.

Primary Presentation	n (%)
Pneumonia*	9 (60%)
Bacteremia	2 (13%)
Meningitis	2 (13%)
Epiglottitis	1 (7%)
Amnionitis	1 (7%)
Total	15

Table 11: Primary Clinical Presentation of	f Invasive Haemophilus influenzae - Alaska, 2012

*with bacteremia

<u>Serotypes</u>

All isolates received at AIP are serotyped; 14 of the 15 cases in 2012 had isolates and were serotyped. The bacterial capsule is the basis for serotyping and is the primary virulence factor. Serotype b was the most common serotype in the past, but its prevalence has decreased with use of the childhood Hib vaccine. Surveillance of serotypes is important for monitoring vaccine effectiveness and emergence of non-vaccine serotypes.

Table 12: Serotypes of Invasive Haemophilus influenzae Cases by Race – Alaska, 2012

		Alaska Native				Non-	Native		
Serotype	Total n (%)	<2	2-18	19-64	65+	<2	2-18	19-64	65+
а	3 (21%)	2	1	0	0	0	0	0	0
b	1 (7%)	0	0	0	1	0	0	0	0
f	4 (29%)	0	0	0	0	0	0	3	1
NT*	6 (43%)	2	0	3	0	0	0	1	0
Total	14	4	1	3	1	0	0	4	1

*Non-typeable

<u>Hib</u>

In recent years, the prevalence of *H. influenzae* type b has declined due to increased use of a childhood vaccine against this serotype. One case of Hib occurred in 2012 in an older adult.

<u>Hia</u>

Prior to 2002, *H. influenzae* type a (Hia) had not been detected in Alaska. Following an outbreak in 2003 [9], cases have occurred sporadically until 2010 when an outbreak began in the YK Delta and continued through 2011 [10]. Three cases of Hia were detected in 2012; all occurred in AK Native children less than 5 years old. The rate of invasive disease caused by Hia in AK Native children less than 2 years old for 2012 was 32.3/100,000.

Antibiotic Resistance

Fourteen *H. influenzae* isolates received at AIP were tested for susceptibility to chloramphenicol, ceftriaxone and TMP/sulfa. All 14 isolates were susceptible to ceftriaxone, one isolate had intermediate resistance to chloramphenicol, and 5 isolates were fully resistant to TMP/sulfa, 5 had intermediate resistance and 4 were susceptible.

Sex	Age (Yrs)	Race	Residence	Site of Isolation	Clinical Presentation(s)	Serotype*	Associated Risk Factors	Survived
М	0.4	AK Native	Other	Blood	Pneumonia	NT	None	No
М	0.6	AK Native	Other	Blood	Meningitis, pneumonia, cellulitis	a	None	Yes
М	0.7	AK Native	Other	Blood	Meningitis	a	None	Yes
М	1.3	AK Native	Other	Blood	Pneumonia	NT	None	Yes
М	4.2	AK Native	Other	Blood	Bacteremia	a	None	Yes
F	30.5	AK Native	Other	Other	Amnionitis	NT	Smoking, alcohol abuse	Yes
М	50.3	AK Native	Anchorage	Blood	Bacteremia	Unknown	Smoking, alcohol abuse	Yes
F	51	Non-Native	Anchorage	Blood	Pneumonia	f	Smoking, chronic lung disease	Yes
F	52.4	Unknown	Anchorage	Blood	Pneumonia	f	Smoking	Yes
М	55.1	AK Native	Anchorage	Blood	Pneumonia	NT	Alcohol abuse	Yes
F	59.1	AK Native	Other	Blood	Pneumonia	NT	Smoking, alcohol abuse	Yes
М	61	Unknown	Anchorage	Blood	Pneumonia	NT	Chronic lung disease	Yes
F	62.1	Non-Native	Other	Blood	Epiglottitis	f	None	Yes
F	68.9	Non-Native	Anchorage	Blood	Pneumonia	f	None	Yes
М	78.9	AK Native	Other	CSF	Pneumonia	b	None	Yes

Table 13: Summary of Invasive Haemophilus influenzae Case Characteristics, Alaska, 2012

*NT = non-typeable

Invasive Neisseria meningitidis

Overall Incidence

Two cases of invasive *Neisseria meningitidis* were reported to AIP in 2012 for an overall rate of 0.3/100,000. The Alaska rate is slightly higher than the ABCs 2012 national projected rate of 0.15/100,000 [11]. There were no invasive *N. meningitidis*-related deaths in Alaska in 2012.

Race

Table 14: Invasive Neisseria meningitidis Cases by Race – Alaska, 2012							
	Cases	Age Adjusted		Deaths			
Race	n (%)	Rate*	% Male	n (%)			
Alaska Native	1 (50%)	0.5	100%	0(0%)			
Non-Native	1 (50%)	0.2	0%	0 (0%)			
Total	2		50%	0 (0%)			

*Cases per 100,000 per percent distribution of Alaska 2010 population

In 2012, 50% of the cases occurred in Alaska Natives. Age-adjusted rates were calculated for Alaska Natives and non-Natives. The age-adjusted rate ratio of *N. meningitidis* disease for the Alaska Native population compared with the non-Native population in 2012 was 2.5.

Sex	Age (Yrs)	Race	Residence	Site of Isolation	Clinical Presentation(s)	Serogroup	Associated Risk Factors	Survived
F	0.3	Non-Native	Other	CSF	Meningitis	В	None	Yes
М	18	AK Native	Anchorage	Blood	Meningitis	В	None	Yes

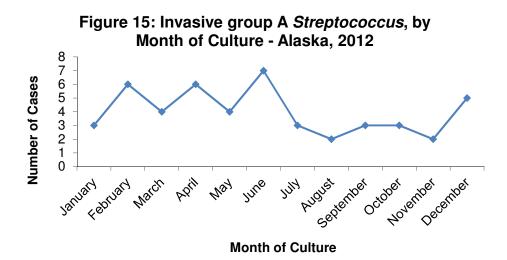
Invasive group A Streptococcus

Overall Incidence

A total of 48 cases of invasive group A *Streptococcus* (GAS) were reported to AIP in 2012. The overall rate of invasive GAS disease in the state of Alaska was 6.6/100,000 persons per year. The Alaska rate is higher than the ABCs 2012 national projected rate of 3.4/100,000 [12]. In 2012, there were 4 GAS-related deaths for a case fatality ratio of 8%.

Seasonality

Cases of group A *Streptococcus* occurred throughout the year in 2012 with no apparent trends in seasonality. The largest number of cases (n=7) occurred in June.



Race

In 2012, 40% of invasive GAS cases in Alaska occurred in the Alaska Native population. The age-adjusted rate ratio of invasive GAS disease for the Alaska Native population compared with the non-Native population in 2012 was 3.1.

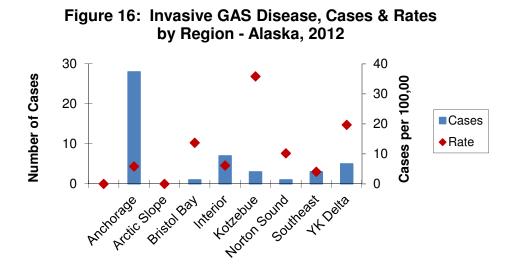
Table 16:	Invasive group	A Streptococcus	Cases by Race -	- Alaska, 2012

	Cases	Age Adjusted		Deaths
Race	n (%)	Rate*	% Male	n (%)
Alaska Native	19 (40%)	14.7	26%	2 (11%)
Non-Native	29† (60%)	4.7	48%	2 (7%)
Total	48		40%	4 (8%)

*Cases per 100,000 per percent distribution of Alaska 2010 population †Includes four cases for which race is unknown

Region

Twenty-eight (58%) of the 48 invasive group A *Streptococcus* cases in 2012 were reported in the Anchorage area, 7 cases in the Interior, 5 cases in the YK Delta, 3 cases each in Kotzebue and Southeast and one case each in Bristol Bay and Norton Sound. The highest rates of disease occurred in the Kotzebue region (35.8/100,000) and the YK Delta (19.6/100,000).



Age

Invasive group A Streptococcus cases reported in 2012 ranged in age from 3 months to 87.5 years old; the median age was 49.7 years. Highest rates of disease occurred in children less than 2 years old (13.9/100,000) and adults 65 years and older (14.1/100,000).

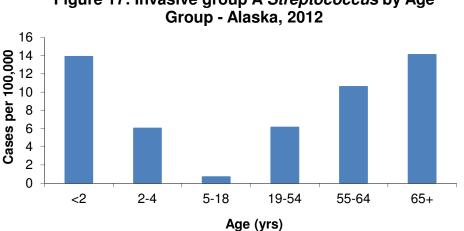


Figure 17: Invasive group A Streptococcus by Age

When stratified by race, the highest rates of invasive group A streptococcal disease occurred in Alaska Native children less than two years old (48.4/100,000 persons per year). The highest

GAS disease rate in the non-Native population occurred in adults 65 and older (11/100,000 persons per year).

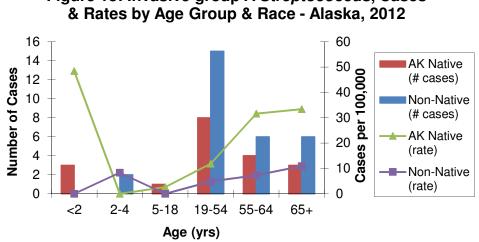


Figure 18: Invasive group A Streptococcus, Cases

Clinical Presentation

The primary clinical presentation was determined by a review of the discharge diagnoses in each patient's individual medical record associated with the invasive bacterial illness. In cases with multiple discharge diagnoses, the most serious diagnosis related to the GAS infection was recorded as the primary clinical presentation. Table 17 shows the primary clinical presentations of invasive group A Streptococcus in Alaska for 2012. Eleven cases also presented with secondary diagnoses including pneumonia, septic arthritis and cellulitis.

Group A Streptococcus was isolated from blood samples in 42 (87.5%) of 48 cases, four from joint fluid and two from a surgical specimen.

Primary Presentation	n (%)
Bacteremia	13 (27%)
Cellulitis*	11 (23%)
Necrotizing fasciitis	6 (13%)
Pneumonia*	4 (8%)
Septic arthritis	4 (8%)
Endocarditis	2 (4%)
Empyema	2 (4%)
Strep toxic shock	1 (2%)
Pericarditis	1 (2%)
Amnionitis	1 (2%)
Endometritis	1 (2%)
Bursitis	1 (2%)
Other	1 (2%)
Total	48

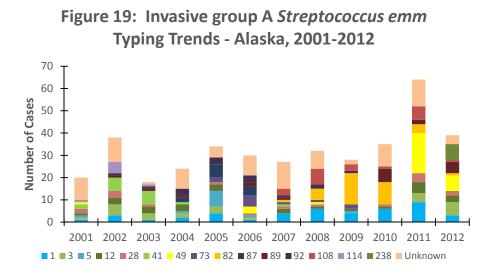
Table 17: Primary Clinical Presentations of Invasive group A Streptococcus – Alaska, 2012

*with bacteremia

Molecular Typing

Strain characterization of GAS has traditionally been based on serological identification of the M protein which is a major surface protein and an important GAS virulence factor. In the mid-1990s, many reference labs started using a molecular approach based on sequencing of the N-terminal region of the M protein gene (*emm* gene). To date, more than 200 different *emm* types have been reported. While there are currently no vaccines available to protect against invasive GAS disease, baseline data on the burden of GAS disease to include *emm* typing are critical to evaluate the potential utility of any candidate vaccines.

In 2012, 38 invasive GAS isolates were *emm* typed at AIP. The most common *emm* types were *emm* 49 and *emm* 238 (18% each), followed by *emm* 3 (16%) and *emm* 89 (13%). The following graph shows *emm* typing trends over time. Strains that totaled \leq 5 over the time period were not included.



Associated Risk Factors

The presence of one or more associated risk factors was reported in 71% of invasive GAS cases in 2012. Diabetes was the most prevalent risk factor observed in adults followed by cigarette smoking and alcohol abuse.

Table 18: Associated Risk Factors Identified in Invasive GAS Cases – Alaska, 2012*

	Adult Cases (≥ 18 years)
Risk Factor	n=44, Cases (%)
Diabetes	13 (31%)
Cigarette smoking	12 (29%)
Alcohol abuse	11 (26%)
Chronic lung disease	6 (14%)
Immunosuppressive treatment	4 (10%)
Injection drug use	0 (0%)
Asplenia	0 (0%)

*More than one risk factor was identified in several cases

Antibiotic Resistance

Forty-three GAS isolates received at AIP were tested for susceptibility to penicillin, ceftriaxone, erythromycin, vancomycin, levofloxacin and clindamycin. All isolates tested were susceptible to penicillin, ceftriaxone, vancomycin, levofloxacin and clindamycin. Four isolates were resistant to both erythromycin; two isolates were *emm* 75, and one each were *emm* 3 and *emm* 58.

	Age			Site of		emm		
Sex	(yrs)	Race	Residence	Isolation	Clinical Presentation(s)	Туре	Associated Risk Factors	Survived
F	0.3	AK Native	Other	Blood	Cellulitis	58	None	Yes
F	0.3	AK Native	Other	Blood	Cellulitis, other	49	None	Yes
F	1.1	AK Native	Other	Blood	Necrotizing fasciitis, cellulits	238	Chronic lung disease	Yes
М	2	Non-Native	Anchorage	Blood	Pneumonia	1	None	Yes
M	3.1	Non-Native	Anchorage	Blood	Empyema, pneumonia	12	None	Yes
7	17.4	AK Native	Other	Blood	Endometritis	75	Chronic lung disease	Yes
7	20.4	Unknown	Anchorage	Blood	Bacteremia	1	None	Yes
M	22.5	AK Native	Anchorage	Joint fluid	Bacteremia	49	None	Yes
М	24.5	Non-Native	Anchorage	Surgical specimen	Empyema, pneumonia	238	Chronic lung disease	Yes
7	27.1	Non-Native	Anchorage	Blood	Bacteremia	49	Immune suppressive treatment	Yes
7	28.6	Unknown	Anchorage	Blood	Amnionitis	3	None	Yes
Λ	29.7	AK Native	Other	Blood	Other	ND	None	Yes
7	35	AK Native	Anchorage	Blood	Cellulitis	49	Alcohol abuse	Yes
Л	38.4	AK Native	Anchorage	Blood	STSS, other	238	Smoking, alcohol abuse	Yes
1	40.7	Non-Native	Other	Blood	Cellulitis	89	None	Yes
1	44.6	Non-Native	Other	Joint fluid	Bursitis	12	Smoking, alcohol abuse	Yes
7	44.9	Non-Native	Anchorage	Blood	Cellulitis	82	Smoking, alcohol abuse, diabetes	Yes
1	45.1	Non-Native	Anchorage	Joint fluid	Necrotizing fasciitis, cellulitis, bursitis	89	Smoking, alcohol abuse	Yes
1	46	Non-Native	Other	Blood	Necrotizing fasciitis, cellulitis	78	None	Yes
1	46.1	AK Native	Other	Surgical specimen	Necrotizing fasciitis, cellulitis	89	Smoking	Yes
Л	46.5	AK Native	Anchorage	Joint fluid	Necrotizing fasciitis, cellulitis	91	Smoking, alcohol abuse	Yes
Л	47.1	AK Native	Other	Blood	Septic arthritis	ND	Smoking, alcohol abuse, immune suppressive treatment	Yes
Л	48.5	Non-Native	Other	Blood	Cellulitis	49	Smoking	Yes
7	49.6	Non-Native	Anchorage	Blood	Pericarditis, cellulitis	238	Diabetes	Yes
1	49.7	AK Native	Other	Blood	Bacteremia	3	Chronic lung disease, immune suppressive treatment, diabetes	Yes
7	50.9	Non-Native	Anchorage	Blood	Cellulitis	238	Immune suppressive treatment	Yes
1	52.6	Non-Native	Anchorage	Blood	Pneumonia	89	Chronic lung disease	Yes
1	54.8	Non-Native	Anchorage	Blood	Bacteremia	28	Smoking, alcohol abuse	Yes
7	54.8	Non-Native	Anchorage	Blood	Cellulitis	1	None	Yes
	60	AK Native	Anchorage	Blood	Bacteremia	19	Alcohol abuse	No
1	60.3	Unknown	Anchorage	Blood	Endocarditis, septic arthritis	94	Smoking, alcohol abuse, diabetes	No
	60.4	Non-Native	Anchorage	Blood	Cellulitis	81	Diabetes	Yes
1	60.5	Non-Native	Anchorage	Blood	Septic arthritis	ND	None	Yes
	61.1	AK Native	Other	Blood	Cellulitis	3	Diabetes	Yes
1	61.8	Non-Native	Other	Blood	Bacteremia	28	None	Yes
	62.6	AK Native	Anchorage	Blood	Bacteremia	49	None	Yes
	63	Non-Native	Anchorage	Blood	Bacteremia	49	None	Yes
	63.7	Non-Native	Anchorage	Blood	Pneumonia	232	Diabetes	Yes
	64.7	AK Native	Anchorage	Blood	Bacteremia	108	Diabetes	Yes
	65.1	Unknown	Anchorage	Blood	Pneumonia	3	Chronic lung disease, diabetes	Yes
1	67.9	Non-Native	Other	Blood	Necrotizing fasciitis, cellulitis	ND	Smoking, chronic lung disease, diabetes	Yes
1	68.2	Non-Native	Other	Blood	Septic arthritis	12	None	Yes
7	71.6	Non-Native	Other	Blood	Cellulitis	75	None	Yes
7	73.9	Non-Native	Other	Blood	Bacteremia	89	Smoking, alcohol abuse	Yes
7	74.2	AK Native	Other	Blood	Endocarditis	3	Chronic lung disease, diabetes	No

 Table 19: Summary of Invasive group A Streptococcus Case Characteristics, Alaska, 2012

Surveillance of Invasive Bacterial Disease in Alaska, 2012

Sex	Age (yrs)	Race	Residence	Site of Isolation	Clinical Presentation(s)	<i>етт</i> Туре	Associated Risk Factors	Survived
F	75.1	AK Native	Other	Blood	Osteomyelitis, septic arthritis, cellulitis	238	Diabetes	Yes
F	78.1	AK Native	Anchorage	Blood	Cellulitis	238	Diabetes	Yes
М	87.5	Non-Native	Anchorage	Blood	Bacteremia	3	None	No

STSS = Streptococcal toxic shock syndrome ND = typing not done

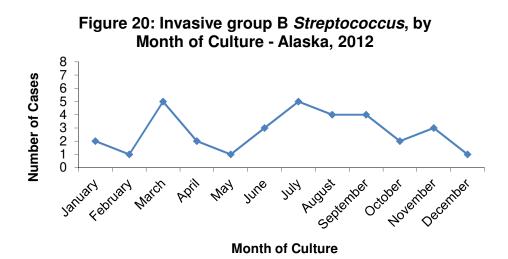
Invasive group B Streptococcus

Overall Incidence

A total of 33 cases of invasive group B *Streptococcus* (GBS) were reported to AIP in 2012. The overall rate of invasive GBS disease in the state of Alaska was 4.5/100,000 persons per year. The Alaska rate is lower than the ABCs 2012 national projected rate of 9/100,000 [13]. In 2012, there were four GBS-related deaths for a case fatality ratio of 12%.

Seasonality

Cases of group B *Streptococcus* occurred throughout the year with no apparent trends in seasonality.



Race

In 2012, 33% of invasive group B *Streptococcus* cases in Alaska occurred in the Alaska Native population; the age-adjusted rate was 8.3/100,000 persons per year which is over two times higher than the non-Native rate of 3.5/100,000 persons per year.

Table 20:	Invasive group	B Streptococcus	Cases by Race -	Alaska, 2012

	Cases	Age Adjusted		Deaths
Race	n (%)	Rate*	% Male	n (%)
Alaska Native	11 (33)	8.3	27	2 (18)
Non-Native	22 (67)‡	3.5	77	2 (9)
Total	33		61	4 (12)

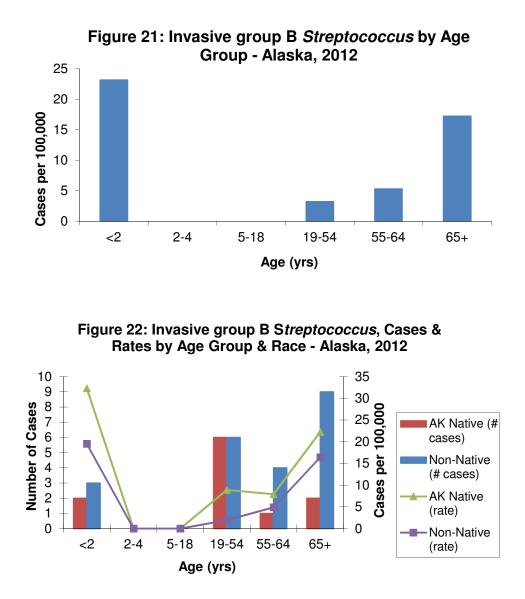
*Cases per 100,000 per percent distribution of Alaska 2010 population ‡Includes three cases for which race was unknown

Region

In 2012, 20 (61%) of the 33 reported GBS cases occurred in Anchorage; five cases were reported in Interior Alaska, three cases each in the YK Delta and Southeast, and one case each in the Arctic Slope and Kotzebue. The highest rates of disease occurred in the Arctic Slope region (11.5/100,000), the Kotzebue region (11.9/100,000) and the YK Delta (11.8/100,000).

Age

Invasive group B *Streptococcus* cases reported in 2012 ranged in age from newborn to 80.9 years old; the median age was 54.6 years. Highest rates of disease overall occurred in children less than two years old (23.2/100,000 persons per year).



When stratified by race, the highest rates of disease occurred in AK Native children less than 2 years of age (32.3/100,000 persons per year). There were three cases of early-onset disease (less than 7 days old) for a rate of 0.3/1,000 live births.

Clinical Presentation

The primary clinical presentation was determined by a review of the discharge diagnoses in each patient's individual medical record associated with the invasive bacterial illness. In cases with multiple discharge diagnoses, the most serious diagnosis related to the GBS infection was recorded as the primary clinical presentation. In 2012, the most common clinical presentation was bacteremia which occurred in 10 cases (30%).

Group B *Streptococcus* was isolated from blood in 30 (91%) of 33 cases in 2012; two cases were isolated from joint fluid and one case from other sterile site.

n (%)
10 (30%)
9 (27%)
4 (12%)
3 (9%)
3 (9%)
1 (3%)
1 (3%)
1 (3%)
1 (3%)
33

Table 21: Primary Clinical Presentations of Invasive group B Streptococcus – Alaska, 2012

*with bacteremia

Antibiotic Resistance

Susceptibility testing was performed on 30 GBS isolates received in 2012. Results of the testing are presented in the following table.

Table 22:	Antibiotic Resistance in	n Invasive group B	3 Streptococcus Isolates	– Alaska, 2012
			- S	

Antibiotic	Susceptible	Intermediate	Resistant	I + R	Total Tested
Penicillin	30 (100%)	0 (0%)	0 (0%)	0 (0%)	30
Ceftriaxone	30 (100%)	0 (0%)	0 (0%)	0 (0%)	30
Erythromycin	12 (40%)	0 (0%)	18 (60%)	18 (60%)	30
Tetracycline	3 (10%)	0 (0%)	27 (90%)	27 (90%)	42
Levofloxacin	29 (97%)	0 (0%)	1 (3%)	1 (3%)	30
Clindamycin	21 (70%)	0 (0%)	9 (30%)	9 (30%)	30
Vancomycin	30 (100%)	0 (0%)	0 (0%)	0 (0%)	30

All isolates tested were susceptible to penicillin, ceftriaxone and vancomycin. Resistance to tetracycline, erythromycin, clindamycin and levofloxacin was seen in 90%, 60%, 30% and 3%,

respectively, of isolates tested. Of the three early onset cases, all isolates were available for susceptibility testing. All three isolates showed resistance to at least one antibiotic. Two of the three isolates tested were resistant to tetracycline; two isolates were resistant to erythromycin and one isolate was resistant to clindamycin.

~		_		Site of			~
Sex	Age (yrs)	Race	Residence	Isolation	Clinical Presentation(s)	Associated Risk Factors	Survived
М	Newborn	Non-Native	Anchorage	Blood	Bacteremia	None	Yes
М	Newborn	Non-Native	Anchorage	Blood	Pneumonia	None	Yes
F	Newborn	AK Native	Other	Blood	Amnionitis	None	No
F	37 days	AK Native	Other	Blood	Bacteremia	None	Yes
М	0.2	Non-Native	Anchorage	Blood	Bacteremia	None	Yes
F	24.5	Unknown	Other	Blood	Cellulitis	None	Yes
F	29.1	AK Native	Anchorage	Blood	Amnionitis, endometritis	Unknown	Yes
F	31	Non-Native	Anchorage	Other	Amnionitis	None	Yes
F	33.6	AK Native	Anchorage	Blood	Cellulitis	Diabetes	Yes
М	34.2	Non-Native	Anchorage	Blood	Cellulitis	Chronic lung disease, diabetes	Yes
F	37.3	AK Native	Anchorage	Blood	Bacteremia	Alcohol abuse	Yes
М	48.2	AK Native	Anchorage	Blood	Empyema, pneumonia	Alcohol abuse, injection drug use	Yes
М	48.9	Unknown	Anchorage	Blood	Cellulitis, osteomyelitis	Diabetes	Yes
F	50.4	Non-Native	Anchorage	Blood	Bacteremia	None	Yes
М	52.6	Non-Native	Other	Blood	Cellulitis, osteomyelitis	Smoking, alcohol abuse	Yes
F	54.1	AK Native	Other	Joint fluid	Other	None	Yes
М	54.6	AK Native	Anchorage	Blood	Bacteremia	Diabetes	Yes
М	57.9	Non-Native	Other	Blood	Endocarditis	Diabetes	Yes
М	59.2	Non-Native	Anchorage	Joint fluid	Septic arthritis	Chronic lung disease, diabetes	Yes
F	59.7	AK Native	Other	Blood	Bacteremia	Immune suppressive treatment	No
М	60	Unknown	Anchorage	Blood	Cellulitis	Diabetes	Yes
F	63.2	Non-Native	Other	Blood	Septic arthritis	Chronic lung disease, diabetes	No
F	65.6	Non-Native	Anchorage	Blood	Pneumonia	None	No
М	66.4	Non-Native	Other	Blood	Cellulitis	Smoking, chronic lung disease, diabetes	Yes
М	66.5	Non-Native	Anchorage	Blood	Bacteremia	None	Yes
М	69.9	Non-Native	Other	Blood	Osteomyelitis	Diabetes	Yes
М	71.9	Non-Native	Anchorage	Blood	Bacteremia	Smoking	Yes
М	73	Non-Native	Anchorage	Blood	Cellulitis	Diabetes	Yes
М	73.1	Non-Native	Anchorage	Blood	Cellulitis	Smoking	Yes
М	73.3	Non-Native	Anchorage	Blood	Pneumonia, osteomyelitis	Diabetes	Yes
F	73.9	AK Native	Other	Blood	Pneumonia	Smoking	Yes
М	78.5	AK Native	Other	Blood	Bacteremia	Unknown	Yes
М	80.9	Non-Native	Other	Blood	Septic arthritis	Alcohol abuse, diabetes	Yes

Table 23: Summary of Invasive group B Streptococcus Case Characteristics, Alaska, 2012

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Appendix

MIC Interpretive Standards Definitions:

CLSI [7] provides recommended interpretive categories for various Minimum Inhibitory Concentration values (cut points) for each organism/antibiotic combination which are defined as follows:

1. Susceptible (S):

The "susceptible" category implies that isolates are inhibited by the usually achievable concentrations of antimicrobial agent when the recommended dosage is used for the site of infection.

2. Intermediate (I):

The "intermediate" category includes isolates with antimicrobial agent MICs that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates. The "intermediate" category implies clinical efficacy applicability in body sites where the drugs are physiologically concentrated (e.g., quinolones and β -lactams in urine) or when a higher dosage of a drug can be used (e.g., β -lactams). The "intermediate" category also includes a buffer zone which should prevent small, uncontrolled technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

3. Resistant (R):

Resistant strains are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules, and/or that demonstrate MICs or zone diameters that fall in the range where specific microbial resistance mechanisms are likely (e.g., β -lactamases) are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.