Epidemiol. Infect. (2002), **129**, 471–478. © 2002 Cambridge University Press
DOI: 10.1017/S0950268802007823 Printed in the United Kingdom

Invasive group A streptococcal infections in the San Francisco Bay area, 1989–99

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(*Accepted 15 July 2002*)

SUMMARY

To describe the epidemiology of invasive group A streptococcal (iGAS) infections in the San Francisco Bay Area, population-based active surveillance for laboratory-confirmed iGAS was conducted by the California Emerging Infections Program in three California counties. From January 1989 to December 1999, 1415 cases of iGAS were identified. Mean iGAS incidence was 4·06/100 000 person-years and case fatality ratio was 13%, with no linear trends over time. Incidence was lowest in adolescents, was higher in men than women (4·4 *vs.* 3·2/100 000 person-years), and was higher in African–Americans (6·7) than in non-Hispanic (4·1) or Hispanic (3·4) Whites, Asians (2·2) or Native Americans (1·7/100 000 person-years). Injecting drug use was the riskiest underlying condition and was associated with the highest attributable risk. Cases were associated with several underlying conditions, but 23% occurred in previously healthy persons. From 1989–1999, iGAS infections in the San Francisco Bay Area became neither more common nor more deadly.

INTRODUCTION

From the early 1900s to the mid-1980s, the incidence of and mortality from invasive group A streptococcal (iGAS) infection and its sequelae declined markedly [1–5]. Since then, clusters of rheumatic fever and iGAS infection and hospital-based case series, as well as increased press attention, have suggested a worldwide resurgence of iGAS disease [6–16]. Several explanations for this apparent resurgence have been proposed, including the spread of more virulent group A streptococcal strains and the increasing prevalence of underlying risk factors [6, 9]. To monitor its incidence and to describe its epidemiologic features, active surveillance for iGAS was undertaken by the California Emerging Infections Program (CEIP). To our knowledge, this is the longest running population-based surveillance system for iGAS in the world.

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METHODS

Laboratory-based active surveillance for selected invasive bacterial infections was established in November 1988 in three counties in Northern California, as part of the Active Bacterial Core Surveillance of the Center for Disease Control and Prevention's Emerging Infections Program. The combined population of the three counties in July 1994 (study midpoint) was 3 170 312 and included residents of Alameda (July 1994 population: 1 449 106), Contra Costa (920 908) and San Francisco (800 298). This population is served by 49 hospitals with clinical microbiology laboratories. From 1 January 1989 to 31 December 1999 the microbiology logs of all 49 hospitals were reviewed for iGAS isolates from normally sterile sites. Beginning 1 January 1990 and continuing to 31 December 1999, active surveillance was conducted for culture-confirmed iGAS.

A contact person (e.g. an infection control practitioner or microbiology supervisor who was responsible for reporting cases to CEIP) was designated for each hospital. Cases were identified either from biweekly telephone calls placed by CEIP staff to contact persons or from review of monthly microbiology department records. Missing information was pursued through telephone interviews with physicians and by medical record review. Laboratories were audited annually or bi-annually to assure that all cases were detected. These audits revealed that the sensitivity of case reporting varied between laboratories from 85 to 95%; unreported cases detected during audits were added to the study. Clinical isolates were identified as GAS by the hospital laboratories using standard methods. An iGAS infection was defined as recovery of GAS from a normally sterile site (e.g. blood, cerebral spinal fluid, synovial fluid or surgical biopsy of deep tissues), or by recovery of GAS from a wound culture in the setting of streptococcal toxic shock syndrome or necrotizing fasciitis. From 1994 to 1999, $>85\%$ of iGAS isolates were sent to the Streptococcus Reference Laboratory of the Centers for Disease Control and Prevention for strain typing. Typing was performed by DNA amplification followed by sequencing of the *emm* gene, using standard methods [17].

Yearly incidence rates of iGAS infection in cases per 100 000 persons per year (cases/10^5 p-y) were calculated by dividing the number of cases by the race-, age-, sex-, and/or county-specific populations as estimated by the 1990 US census or the yearly intercensal projections [18]. Other incidence rates were calculated using intercensal population projections for July 1994 (the midpoint of the study). Because risk factor data from medical charts were coded differently in 1997 than in all other years, data for underlying medical conditions (e.g. diabetes mellitus, alcoholism, and malignancy) among iGAS cases were not available for 1997 cases. The population prevalence of these underlying conditions were estimated using disease-specific public health databases (e.g. California Department of Health Services, American Lung Association, American Diabetes Association, American Cancer Society). Estimates of risk (prevalence ratios) were then calculated for these underlying conditions: the prevalence of each underlying condition in iGAS cases was divided by the point prevalence of that condition in the study population (see Table 1). The (unadjusted) attributable risk associated with each risk factor was calculated as [19]:

$$\frac{\text{Prevalence among iGAS cases} \times (\text{prevalence ratio} - 1)}{\text{prevalence ratio}}.$$

Differences in proportions were analysed using the χ^2 test with the Yates correction or the Fisher exact test; differences in continuous variables were performed using the Wilcoxon two-sample test; and trend analyses were performed using the χ^2 test for linear trend (Epi-Info 6.04; CDC, Atlanta, GA, USA). Seasonality was assessed using a modification of the Hewitt test [20].

RESULTS

We identified 1415 cases of iGAS disease from January 1989 to December 1999. The overall incidence rate was 4·06/10^5 p-y (95% CI, 3·9–4·3). The overall case-fatality ratio was 13·3% (95% CI, 11–15%). No linear trend was detected in the incidence of iGAS infection or in the case-fatality ratio, although the data suggest that incidence peaks every 5 years (Fig. 1). The incidence of iGAS was higher in San Francisco County (6·7/10^5 p-y; 95% CI, 6·2–7·3) than in Alameda County (2·9/10^5 p-y; 95% CI, 2·6–3·1) or Contra Costa County (2·7/10^5 p-y; 95% CI, 2·4–3·1). iGAS infections were more common among males (4·4/10^5 p-y; 95% CI, 4·1–4·7) than females (3·2; 95% CI, 3·0–3·5). Compared to African–Americans (6·8; 95% CI, 6·1–7·6) the incidence of iGAS was lower among non-Hispanic Whites (4·1; 95% CI, 3·8–4·5), Hispanic Whites (3·4; 95% CI, 2·9–4·0), Asian/Pacific Islanders (2·2; 95% CI, 1·8–2·6), and Native Americans (1·7; 95% CI, 0·5–4·4).

The median age of patients with iGAS was 44 years (1 day–98 years). The incidence of iGAS reached a nadir among children aged 10–14 years, then increased

Table 1. *Frequency and case-fatality ratio of various clinical presentations of iGAS infection, October 1994 to December 1999*

Clinical syndrome	Patients with syndrome	Case-fatality ratio
Soft tissue infections	293/660 (44 %)	22/290 (8 %)
Cellulitis alone	223/660 (34 %)	14/222 (6 %)
Abscess alone	24/660 (4 %)	0/23 (0 %)
Necrotizing fasciitis alone	21/660 (3 %)	3/20 (15 %)
Necrotizing fasciitis with cellulitis or abscess	25/660 (4 %)	5/25 (20 %)
Bacteraemia without known source	144/660 (22 %)	25/144 (17 %)
Pneumonia	65/660 (10 %)	13/65 (20 %)
Streptococcal toxic shock syndrome	32/661 (5 %)	14/31 (45 %)
Meningitis	8/661 (1 %)	3/7 (43 %)

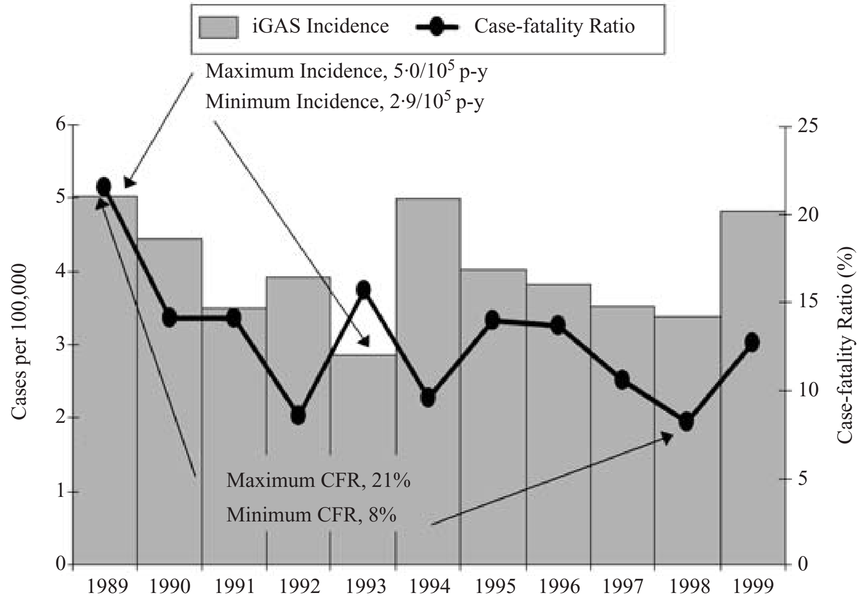

Fig. 1. Incidence of iGAS and case-fatality ratio (CFR) among iGAS cases in the San Francisco Bay area by year: 1989–99.

with age ($P<0{\cdot}001$) (Fig. 2). The incidence of invasive GAS was 29 % higher in December, January, February and March than during the rest of the year; more cases occurred in each one of those months than in any other month ($P<0{\cdot}003$) (Fig. 3). Underlying medical conditions and risky behaviours were common among iGAS cases (Table 2). Of those cases for which information was obtained, the medical record noted alcohol abuse in 24 %, injecting drug use in 24 %, diabetes mellitus in 20 %, antecedent trauma in 19 %, heart disease in 11 %, malignancy, excluding basal or squamous cell skin cancers, in 15 %, lung disease in 15 %, and HIV or AIDS in 7 %. Injecting drug use was the riskiest underlying condition (was associated with the highest prevalence ratio) and accounted for the most cases (was associated with the highest attributable risk). However, heart disease was associated with the highest prevalence ratio among persons less than 50 years old, and the highest attributable risk among persons more than 50 years old. Chronic obstructive pulmonary disease was not shown to be a risk factor for iGAS. In 106 (23 %) of 471 fully investigated cases, none of the above underlying conditions were noted.

To investigate whether the county, race, and sex-specific incidence rates of iGAS paralleled the distributions of underlying conditions, the prevalence of underlying conditions were compared by county (San Francisco *vs.* others), by racial group (Black or Asian *vs.* all others) and by gender (Fig. 4). Residents of San Francisco were more likely to have had at least

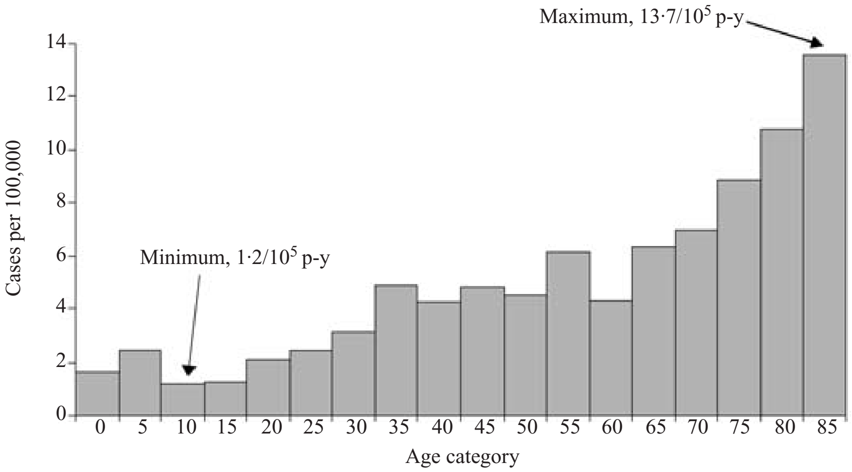

Fig. 2. iGAS incidence in the San Francisco Bay Area by 5-year age categories: 1989–99. Each category includes the named year and the 4 years above it, e.g. age category 35 includes all persons 35–39 years of age, inclusive. Age category 85 includes persons 85–99 years of age, inclusive.

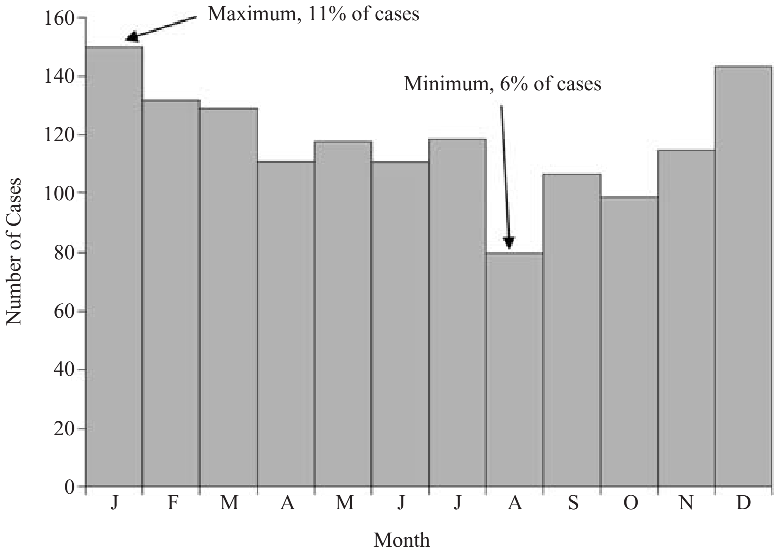

Fig. 3. Number of iGAS cases in the San Francisco Bay area by month: 1989–99.

one underlying condition (83%) than were residents of Alameda (74%, $P = 0{\cdot}04$) or Contra Costa (72%, $P = 0{\cdot}03$) counties. Asian/Pacific Islanders (58%) were less likely to have had at least one underlying condition than African–Americans (82%, $P = 0{\cdot}002$) or members of other racial/ethnic groups (78%, $P = 0{\cdot}003$). African–Americans and others were about equally likely to have at least one underlying condition ($P = 0{\cdot}5$). The percentage of men (82%) who had at least one underlying condition was higher than for women (71%, $P = 0{\cdot}004$). To evaluate whether these results were applicable to our study population, we compared the demographic characteristics of the 374 (26%) patients in whom detailed risk-factor data was obtained to the 1041 without risk-factor data. The racial, ethnic, and gender composition of the two groups were nearly identical. However, patients with available risk factor data were younger than those without such data (median, 43 *vs.* 47 years, $P = 0{\cdot}01$).

Case-fatality ratios were similar for all racial and ethnic groups ($P > 0{\cdot}05$ for all pairwise comparisons) and did not vary by county. Case-fatality ratios were elevated among persons with underlying cardiac disease (29 *vs.* 9%, $P < 0{\cdot}001$) or malignancy (26 *vs.* 11%, $P = 0{\cdot}006$) but were otherwise unaffected by the presence or absence of other risk factors.

From October 1994 to December 1999, detailed clinical data were collected from iGAS cases (Table 1).

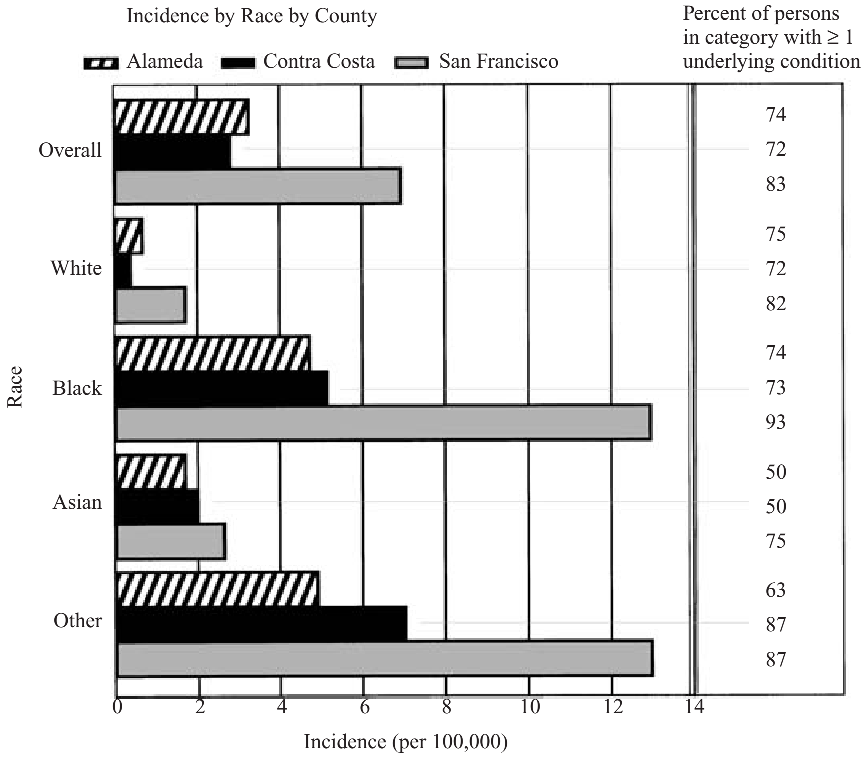

Fig. 4. iGAS incidence in the San Francisco Bay area by race and county: 1989–99. To assess whether the variation in incidence between race-county categories could be due to the risk factor profile of these categories, incidence rates (horizontal bars) are shown adjacent to the percent of cases in that grouping with $\geqslant 1$ underlying condition (numbers on right side of figure).

Patients with iGAS most commonly developed soft tissue infections, either with [46 (7%) of 660 cases] or without [247 (38%) of 660 cases] necrotizing fasciitis. The most deadly clinical presentation was STSS. Of patients with iGAS during this interval with available clinical data, 32 (5%) of 661 had STSS by the CDC case definition [20], and 14 (45%) of 31 died. During the same interval, five patients (1, 3, 4, 27 and 43 years of age) had been diagnosed with chickenpox in the month before their positive iGAS culture.

Of 662 iGAS isolates from which an *emm* sequence was obtained during 1994–1999, the most common *emm* types were *emm* type 1 (16%), *emm* type 3 (7%), *emm* type 12 (7%), *emm* type 28 (6%) and *emm* type ST-2967 (8%). The frequency of these strains was relatively constant over the study period, and did not increase in 1994 or 1999 (the years of highest iGAS incidence during those six years).

DISCUSSION

We describe the results from the longest running population-based active surveillance for iGAS in the United States. Our study addresses recent public health concerns about a resurgence of this disease, demonstrating no linear increase in the incidence of iGAS in this three-county area from 1989 to 1999. It also confirms previous findings that iGAS infections occur more commonly in the winter [21]. In addition, these data suggest recurring 5-year peaks in incidence that should be explored by continuing surveillance and molecular subtyping of isolates.

A higher incidence of iGAS among men was noted in our study, in contrast to other reports in which the majority (up to 63%) of patients were female, though these were not population-based studies [22, 23]. The higher incidence of iGAS in males that we observed might be accounted for by the excess of alcohol abuse (Table 2) and other risk factors among men. However, we do not have sufficiently detailed information about the population under surveillance to draw firm conclusions. In addition, since our risk factor data was obtained from a subset of our study sample that was a median of 4 years younger than the rest of the sample, it is possible that our study overestimates the percent of cases attributable to cofactors more

Table 2. *Distribution of underlying conditions among iGAS cases*

	Underlying condition							
	Alcohol abuse[a]	Injecting drug use[b]	Diabetes mellitus[c]	Heart disease[d]	Lung disease[e]	Cancer[f]	HIV or AIDS[g]	Trauma
County								
San Francisco (*n* = 800 298)[h]	32 % (62/193)	35 % (67/192)	14 % (27/191)	20 % (38/189)	11 % (21/187)	13 % (25/187)	10 % (20/198)	15 % (28/185)
Contra Costa (*n* = 920 908)	15 % (14/93)	13 % (12/92)	23 % (22/96)	19 % (18/95)	17 % (16/93)	20 % (19/96)	3 % (3/91)	18 % (17/94)
Alameda (*n* = 1 449 106)	18 % (22/125)	14 % (17/124)	26 % (31/121)	19 % (22/118)	19 % (23/123)	13 % (15/120)	4 % (5/117)	26 % (30/117)
Race/ethnicity								
White non-Hispanic (*n* = 1 634 329)	22 % (49/219)	25 % (54/220)	13 % (27/216)	22 % (48/217)	17 % (36/217)	16 % (34/217)	6 % (12/213)	20 % (39/193)
White Hispanic (*n* = 429 267)	41 % (16/39)	29 % (10/35)	14 % (5/36)	9 % (3/34)	12 % (4/34)	6 % (2/34)	6 % (2/34)	30 % (11/37)
Black (*n* = 450 235)	32 % (28/87)	30 % (27/89)	26 % (22/84)	13 % (11/83)	14 % (12/85)	10 % (8/84)	13 % (11/85)	19 % (16/85)
Native American (*n* = 23 035)	50 % (1/2)	50 % (1/2)	0 % (0/2)	0 % (0/2)	0 % (0/2)	50 % (1/2)	0 % (0/2)	0 % (0/2)
Asian (*n* = 633 446)	0 % (0/44)	2 % (1/44)	34 % (17/50)	31 % (15/48)	9 % (4/44)	18 % (8/44)	2 % (1/44)	9 % (4/46)
Sex								
Female (*n* = 1 602 729)	10 % (16/165)	22 % (37/170)	17 % (28/168)	17 % (29/167)	14 % (23/147)	17 % (29/167)	5 % (8/165)	15 % (25/166)
Male (*n* = 1 567 583)	33 % (82/246)	25 % (59/238)	22 % (52/240)	21 % (49/235)	16 % (37/233)	13 % (30/236)	9 % (20/232)	22 % (50/230)
Overall								
Prevalence in iGAS[i]	24 % (98/411)	24 % (96/408)	20 % (80/408)	< 50 yrs: 5·0 % (11/219) ⩾ 50 yrs: 36·6 % (67/183)	15 % (16/403)	15 % (59/403)	7 % (28/397)	19 % (75/396)
Population prevalence	4·5 %	1·7 %	7·3 %	< 50 yrs: 0·09 % ⩾ 50 yrs: 2·2 %	11·2 %	0·5 %	1·5 %	NA[j]
Prevalence ratio[k]	3·8 (3·0–4·7)	16 (12·1–20·5)	2·0 (1·6–2·6)	50 (27·2–91·6) 14·5 (11·5–18·4)	1·0 (0·7–1·3)	16 (11·7–22·6)	5·9 (4·2–8·2)	NA
Attributable risk[l]	0·18	0·23	0·13	< 50 yrs: 0·05 ⩾ 50 yrs: 0·34 All ages: 0·18	0	0·14	0·06	NA

Notes to Table 2

[a] *California Behavioral Risk Factor Survey, 1995*. California Department of Health Services (CDHS). Self-reported chronic drinkers of more than 60 drinks per month.

[b] Shafer KP, McFarland W, Katz MH San Francisco Department of Public Health HIV Seroepidemiology Unit, 1997 HIV Consensus Report on HIV Prevalence and Incidence in San Francisco, Summary Table 6, p. 18 (unpublished).

[c] American Diabetes Association, 1994. Statewide data used to estimate the number of diabetics in the study area.

[d] California Office of Statewide Health Planning Data, CDHS, 1995. 'Heart disease' included both a history of acute myocardial infarction, of document ischaemic coronary artery disease, and/or physician-diagnosed CHF.

[e] American Lung Association, 1996.

[f] Cancer Surveillance Section, CDHS, 1993. Basal and squamous cell skin cancers not included.

[g] Seroepidemiology and Surveillance Branch, Office of AIDS, San Francisco County Department of Public Health, 1996. *Note*: Only iGAS cases from San Francisco are included.

[h] Total number of persons of this demographic category in the surveillance population, according to the US Census Bureau July 1994 intercensal estimates (http://www.census.gov/population/estimates/county/casrh/casrh06.txt).

[i] Prevalence in iGAS is the number of times in which the underlying condition was noted to be present in the medical chart, divided by the number of times that the condition was noted to be either present or to be not present. Cases from 1997 were excluded.

[j] Data not available.

[k] Prevalence in iGAS cases during the entire study period (excluding 1997) divided by the point prevalence in the study population, which was estimated from various sources as noted.

[l] Attributable Risk = (Prevalence in iGAS cases) × (Prevalence ratio − 1) ÷ (Prevalence ratio).

common in younger age groups while underestimating, for example, the importance of malignancy, which is more common among the elderly.

A significantly higher incidence of invasive GAS infection was observed among African–Americans that was not accounted for by underlying risk factors. Race may be a surrogate marker for other, unmeasured, factors such as access to health care. Surprisingly, the incidence of iGAS in Native Americans (1·7) in our population was much lower than the incidence (36·5/10^5 p-y) in Native Americans in another population-based study in Arizona [21]. We suspect that this discrepancy is due to the failure of health-care providers in the San Francisco Bay Area to correctly identify Native Americans. A second possibility is that the lower rates seen in this study represent the risk of iGAS infection among a more fully integrated San Francisco Bay Area Native American population. However, a previous study demonstrated that Native Americans living on and those living off reservations had similarly high rates of iGAS infection, so this explanation seems less likely [21].

The incidence and epidemiologic features of this disease have been difficult to monitor in an unbiased fashion. Incidence rates and case-fatality ratios extrapolated from single institutions are unstable and can reflect the biases inherent in voluntary reporting as well as changing referral patterns. Although iGAS infections have recently been made reportable in most public health jurisdictions, passive reporting typically results in an underestimate of incidence.

iGAS infections can progress and kill quickly. Injecting drug use and underlying cardiac disease were the most important risk factors for the disease in our population, but nearly one-quarter of evaluated iGAS patients had no identifiable risk factors. This complicates early recognition and treatment and places a premium on research to: determine immunologic, genetic, or other risk factors for iGAS; optimize new therapies, such as IVIG and protein-synthesis inhibiting antibiotics; evaluate the appropriateness of chemoprophylaxis; develop an effective vaccine; and target high-risk groups for enrollment into vaccine trials [24].

ACKNOWLEDGEMENTS

We thank Ken Vosti and Robert Armstrong for reviewing the manuscript; Nick Czap for technical support; Gretchen Rothrock for programming support.

Data for heart disease was provided courtesy of Kathy McDonald and Mark Hlatky, Division of Cardiology, Stanford University. This project was funded in part through a cooperative agreement from the Centers for Disease Control and Prevention through its Emerging Infections Program.

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