Am. J. Trop. Med. Hyg., 66(1), 2002, pp. 61–70

LEPTOSPIROSIS IN HAWAII, 1974–1998: EPIDEMIOLOGIC ANALYSIS OF 353 LABORATORY-CONFIRMED CASES

ALAN R. KATZ, VERNON E. ANSDELL, PAUL V. EFFLER, CHARLES R. MIDDLETON, AND DAVID M. SASAKI

Department of Public Health Sciences and Epidemiology, John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii; Kaiser-Permanente Medical Center, Honolulu, Hawaii; Epidemiology Branch, Communicable Disease Division, Hawaii State Department of Health, Honolulu, Hawaii

Abstract. The epidemiologic characterization of leptospirosis in the United States has been limited by difficulties associated with both case detection and confirmation. In addition, leptospirosis was eliminated from the list of National Notifiable Diseases in 1995. From 1974 until the cessation of national surveillance, Hawaii consistently had the highest reported annual incidence rate in the United States. From 1974 through 1998, 752 leptospirosis cases were reported in the State of Hawaii. Of these, 353 had exposures within the state and were laboratory confirmed. The mean annual incidence rate was 1.29 per 100,000. Cases were predominately male. Rates were highest in rural areas. Occupational exposures diminished over time while recreational exposures increased. This series represents the first large U.S. leptospirosis surveillance report since 1979. With leptospirosis recently being identified as a re-emerging zoonosis, continued national surveillance and case reporting should be reconsidered.

INTRODUCTION

Leptospirosis is an illness with protean manifestations and world-wide distribution.[1] It has been classified as a re-emerging zoonosis by the World Health Organization.[2] Recently reported outbreaks in Nicaragua,[3] Costa Rica,[4] Brazil,[5] India,[6] the mainland United States,[7] and among participants in the EcoChallenge competition in Borneo[8,9] have refocused attention on this disease. From 1974 through 1994, Hawaii consistently had the highest reported annual incidence rate in the United States.[10–30] Although leptospirosis was deleted from the list of nationally notifiable infectious diseases in 1995,[31] cases remain reportable in the State of Hawaii. This paper describes the epidemiologic characterization of leptospirosis in the State of Hawaii through a detailed analysis of confirmed cases related to exposures within the state.

METHODS

Leptospirosis case investigation reports collected by the Hawaii State Department of Health (DOH) were reviewed for the 25-year period from 1974 through 1998. These reports are generated by DOH epidemiologists for all reported leptospirosis cases in the State, and include demographic, epidemiologic, clinical, and laboratory information obtained from patient interviews, medical record reviews, and laboratory reports of serologic, culture, and fluorescent antibody testing.

Cases were classified as either confirmed, probable, or suspect based on clinical and laboratory findings. A confirmed case had a clinically compatible illness with at least one of the following laboratory criteria for confirmation: four-fold or greater increase in microscopic agglutination test (MAT) titer between acute- and convalescent-phase serum specimens; isolation of *Leptospira* from a clinical specimen; or demonstration of *Leptospira* in a clinical specimen by immunofluorescence.[32,33] Cases were classified as probable if there was a clinically compatible illness with supportive serologic findings (i.e., MAT titer $\geq$ 1:200 in one or more serum specimen without a four-fold increase in titer).[34] Suspect cases were defined as being clinically compatible with laboratory evidence of infection including a positive macroscopic slide agglutination test result, reactive IgM enzyme-linked immunosorbent assay (ELISA), positive indirect hemagglutination assay (IHA), MAT titer $<$ 1:200, or presumptive identification of leptospires in blood, body fluids, or tissue specimens by darkfield microscopy. Only cases classified as confirmed were included in this analysis. The MAT and direct fluorescent antibody testing were conducted by the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. The DOH laboratory conducted isolation procedures using Ellinghausen-McCullough-Johnson-Harris semisolid media. Serogrouping and serotyping of culture isolates were also conducted by the CDC.[32] Technical assistance was received from the Royal Tropical Institute (RTI) in Amsterdam, the Netherlands in 1989 for microscopic agglutination testing and serotyping.

Infecting serogroups were definitively identified on culture isolates but only presumptively identified by MAT, since definitive identification is not possible with MAT due to cross-agglutination/cross-reactivity between serovars of different serogroups.[35] For cases demonstrating a four-fold or higher increase in MAT titer between acute- and convalescent-phase serum specimens, the serogroup showing the highest titer on the convalescent-phase sera was considered to be the presumptive infecting serogroup. If there were more than one serogroup with the same high titers, the presumptive infecting serogroup for the case was designated indeterminate.

Data analysis. Cases were analyzed individually and categorized into five five-year intervals from 1974 to 1998 to assess temporal trends. Frequencies, relative risks, and chi-square tests for linear trend were calculated using Epi Info version 6.04 (CDC, Atlanta, GA). Mid-*P*-corrected 95% confidence intervals and exact *P* values for odds ratios and relative risks, and exact 95% confidence intervals for annual leptospirosis incidence rates using Clopper-Pearson method were calculated using StatXact version 4.0.1. (Cytel Software Corporation, Cambridge, MA). Reference groups selected for comparisons were those subgroups in each category with the largest populace according to the 1990 U.S. Census (ethnicity: Caucasian; age = 30–39 years; island: Oahu).[36] The independent contribution of age, island of exposure, and ethnicity was assessed in a multivariate analysis

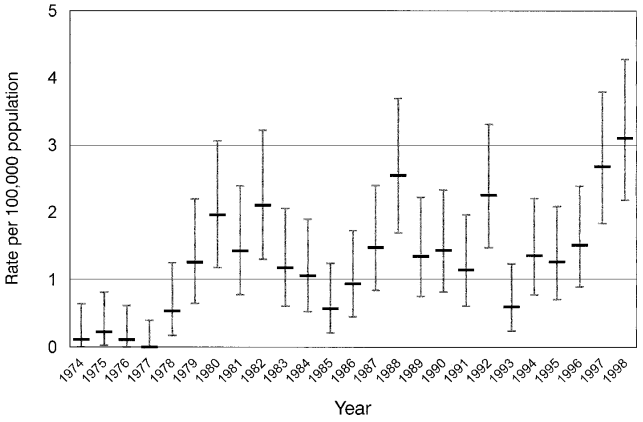

FIGURE 1. Annual confirmed leptospirosis incidence rates, State of Hawaii, 1974–1998. 95% confidence intervals are indicated by brackets.

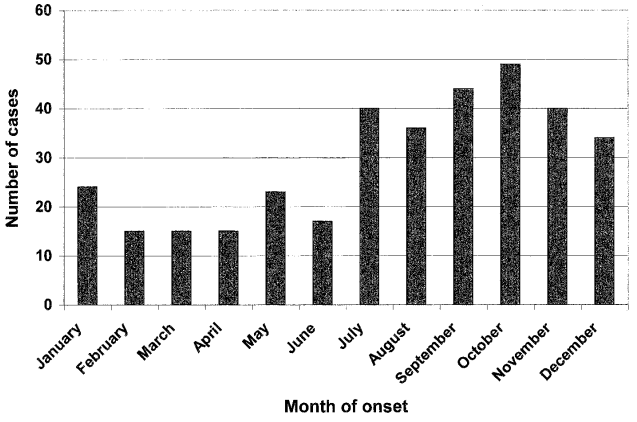

FIGURE 2. Month of onset for 352 confirmed leptospirosis cases, State of Hawaii, 1974–1998.

using logistic regression, where denominators were obtained from aggregate factor-specific Hawaii State data from the 1990 U.S. Census.[36] Odds ratios and likelihood ratio 95% confidence limits were adjusted by a scale factor of 1.149 (based on deviance divided by degrees of freedom) and calculated using the Genmod Procedure of SAS version 8.0. (SAS Institute, Cary, NC). *P* values less than or equal to 0.05 were considered statistically significant. All test were two-tailed.

RESULTS

A total of 752 cases were reported to the DOH during the 25-year period, 1974–1998. Seven hundred nine cases were contracted through exposures within the State of Hawaii, while 43 cases were related to exposures that occurred outside the State. Of the 709 cases of leptospirosis due to exposures within the State, 353 were classified as confirmed; 180 were classified as probable, while 176 were classified as suspect.

The number of confirmed cases reported to the DOH per year ranged from zero (1977) to a high of 37 (1998), with a median of 14 annual case reports, and a mean annual incidence rate of 1.29 per 100,000 population. There was a significant temporal trend in increasing leptospiral incidence rates over this 25-year period (χ^2 for linear trend = 7.89, $P = 0.005$) (Figure 1). The month of occurrence was identified for virtually all cases (352 of 353). Sixty-nine percent (243 of 352) of cases occurred during the late summer, fall, and early winter months (July through December) while 31% (109 of 352) occurred during the late winter, spring, and early summer months (January through June) (Figure 2).

The island of exposure was identified for > 99% of the cases (351 of 353). Most cases were exposed on the island of Hawaii (50%), followed by Kauai (28%), and Oahu (19%), with very few cases reported from the island of Maui (1%). A single case was exposed on each of the following islands: Niihau, Molokai, and Lanai. Cases from the latter three islands were not included in the island-specific rate calculations or multivariate statistical analysis. A comparison of mean annual incidence rates revealed Kauai with the highest rate (7.85 per 100,000) followed by Hawaii (5.85 per 100,000), Oahu (0.32 per 100,000), and Maui (0.22 per 100,000). A comparison of incidence rates on the less populated neighbor islands using Oahu as the reference population, revealed a relative risk of 24.50 for Kauai (95% confidence interval [CI] = 18.00, 33.50) and 18.26 for the island of Hawaii (95% CI = 13.83, 24.32) ($P < 0.0001$ respectively), while the relative risk for exposure on Maui was 0.68 (95% CI = 0.24, 1.58) ($P = 0.55$) (Table 1). In addition to information on island of exposure, an attempt was made to identify the location of exposure, by census tract and district, on each island. The most common locations were census

TABLE 1
Island of exposure for 353 confirmed leptospirosis cases, State of Hawaii, 1974−1998

Island	Number observed (percent)	Estimated mean annual incidence rate (per 100,000)*	Relative risk (mid-*P* corrected 95% confidence interval)	Exact *P* value
Hawaii	176 (50.1%)	5.85	18.26 (13.83, 24.32)	< 0.0001
Kauai	100 (28.5%)	7.85	24.50 (18.00, 33.50)	< 0.0001
Oahu	67 (19.1%)	0.32	1.0 (Reference group)	
Maui	5 (1.4%)	0.22	0.68 (0.24, 1.58)	0.55
Lanai	1			
Molokai	1			
Niihau	1			
(Unknown)	2			
Total	353			

* (Number of cases observed over a 25-year period for a specific island of exposure/25)/island-specific population from 1990 U.S. Census data.[36]

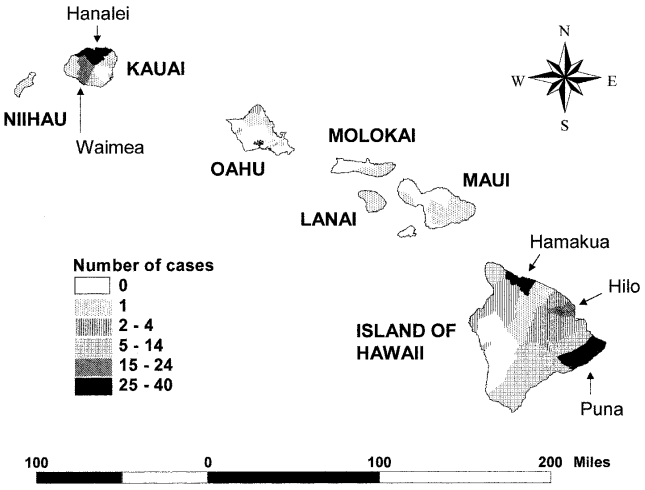

FIGURE 3. Map of census tract exposure location for 292 confirmed leptospirosis cases, State of Hawaii, 1974–1998.

tracts within the following districts: Puna, Hilo, and Hamakua on the island of Hawaii, and Hanalei on Kauai (Figure 3).

Males accounted for 92% of the cases, and the ages of cases ranged from one to 78 years with a median of 33 years. Comparison of age-specific incidence rates revealed persons 20–49 years of age to have the highest rates, and children 0–9 years of age to have the lowest rates (Table 2).

There were five deaths among 353 confirmed cases during this 25-year interval (case fatality rate = 1.4%). Increasing age was associated with an increase in leptospirosis related mortality (χ^2 for linear trend = 5.5, $P = 0.02$).

Information on ethnicity was not routinely obtained for the first 14 years of this study; however, from 1988 through 1998, more than 99% of the cases (222 of 223) were ethnically identified. The majority of reported cases from 1988 through 1998 were Caucasian (55%), followed by Hawaiian/part Hawaiian (17%), Japanese (14%), and Filipino (5%). A comparison of ethnic-specific incidence rates revealed Caucasian, Samoan, and Hawaiian/part Hawaiian to have the highest rates, while Japanese, Filipino, and Chinese persons had the lowest rates. Using Caucasians as the reference group, there were no statistical differences in rates compared with persons of Samoan or Hawaiian/part Hawaiian ethnicity, but persons of Japanese, Filipino, and Chinese ethnicity were at a statistically significant decreased risk of illness compared with Caucasians (Table 3). After adjusting for age and island of exposure, persons of Filipino and Japanese ethnicity remained at a statistically significant decreased risk compared with Caucasians. Small population subgroup sizes disallowed the inclusion of Samoan or Chinese ethnic categories within the logistic regression analysis (Table 4).

Information allowing for an exposure classification was possible for 95% (335 of 353) of the cases. Occupationally related exposures were reported for 41% (137 of 335), while 43% (143 of 335) of the cases were exposed through recreational activities. Habitational exposures (exposures around the home) accounted for 16% (55 of 335) of the cases. The proportion of cases exposed recreationally increased over time (χ^2 for linear trend = 8.1, $P = 0.004$), while occupational exposures demonstrated a proportional decrease ($\chi^2 = 10.5$, $P = 0.001$) (Figure 4).

Of those individuals occupationally exposed, 77% (106 of 137) were agricultural workers. Individuals with recreational exposures listed swimming (59%), hiking and/or camping (19%), prawning (15%), and hunting (10%). Less common recreational activities included waterskiing on a river, mudsliding, and cross country running. A single case reported canoeing on a river (Table 5).

Information on animal exposures was obtained from 228 cases. Reported exposures were recorded with decreasing frequency for the following animals: dogs (71%), cats (34%), rodents (30%), cattle (23%), swine (15%), and horses (12%). The sum exceeds 100% since more than 40% of the cases reported multiple animal exposures.

Most (334 of 353) cases occurred sporadically and were unrelated, although six laboratory-confirmed outbreaks were reported during this 25-year period, each involving from two to eight persons. Three were occupationally related, involving dairy, ginger, and taro farmers, and three involved recreational exposures. The largest outbreak involved eight of 16 young men regularly swimming in a river over a two-week period[37] (Table 6).

Of 207 cases for which information relating to the presence or absence of skin wounds during the incubation period was obtained, 170 (82%) reported skin wounds.

Among confirmed cases, 81 (23%) of 353 were diagnosed by culture isolates from the following clinical specimens: 66

TABLE 2
Age group of 353 confirmed leptospirosis cases, State of Hawaii, 1974–1998

Age group (years)	Number observed (%)	Estimated mean annual incidence rate (per 100,000)*	Relative risk (mid-*P* corrected 95% confidence interval)	Exact *P* value
0–9	5 (1.42)	0.12	0.07 (0.03, 0.16)	< 0.0001
10–19	49 (13.92)	1.34	0.77 (0.54, 1.10)	0.18
20–29	89 (25.28)	1.86	1.08 (0.80, 1.45)	0.68
30–39	85 (24.15)	1.73	1.0 (Reference group)	
40–49	73 (20.74)	2.02	1.17 (0.85, 1.60)	0.38
50–59	26 (7.39)	1.13	0.65 (0.41, 1.00)	0.06
60–69	15 (4.26)	0.64	0.37 (0.21, 0.62)	0.00012
70–79	10 (2.84)	0.72	0.41 (0.20, 0.77)	0.0054
(Unknown age)	1			
Total	353			

* (Number of cases observed over a 25-year period for a specific age group/25)/age-group specific population from 1990 U.S. Census data.[36]

TABLE 3
Ethnicity of 222 confirmed leptospirosis cases, State of Hawaii, 1988–1998

Ethnicity	Number observed (%)	Estimated mean annual incidence rate (per 100,000)*	Relative risk (mid-*P* corrected 95% confidence interval)	Exact *P* value
Caucasian	122 (55.0%)	3.00	1.0 (Reference group)	
Hawaiian/ part Hawaiian	37 (16.7%)	2.42	0.81 (0.55, 1.16)	0.29
Japanese	30 (13.5%)	1.10	0.37 (0.24, 0.54)	< 0.0001
Filipino	12 (5.4%)	0.65	0.22 (0.11, 0.38)	< 0.0001
Samoan	5 (2.3%)	3.02	1.01 (0.36, 2.29)	1.00
Chinese	2 (0.9%)	0.26	0.09 (0.01, 0.30)	< 0.0001
Mixed ethnicity	5 (2.3%)			
Other race	9 (4.1%)			
Total	222			

* (Number of cases observed over an 11-year period for a specific ethnic group/11)/ethnic-specific subgroup population from 1990 U.S. Census data.[36]

blood, 6 urine, 2 cerebrospinal fluid (CSF), 1 blood and urine, 1 blood and CSF, and 5 unspecified source. The 81 cases with culture isolates included 48 with diagnostic MAT results and 33 diagnosed by culture isolate alone. Two hundred seventy cases were diagnosed serologically without culture isolates, and two cases demonstrated antibodies to *Leptospira* in post-mortem tissue specimens using a direct fluorescent antibody test. Seventy-five (93%) of the 81 culture isolates had definitive serovar or serogroup identification. Serovars in the Icterohaemorrhagiae serogroup were the most common, accounting for 43 (57%) of the 75 identified isolates. Culture isolates came from cases on the islands of Hawaii, Kauai, Oahu, and Niihau. Serovars in the Australis serogroup were the second most common isolate accounting for 19 (25%) of the 75 identified isolates, with isolates coming from cases on the islands of Hawaii, Kauai, and Oahu. Serovars in the Bataviae and Ballum serogroups accounted for 7% each. Serovars in the Ballum serogroup were only isolated from cases on the island of Hawaii, while serovars in the Bataviae serogroup were isolated from cases on Oahu, Kauai, and Maui (Table 7). A new serovar from the Bataviae serogroup was isolated from a patient on the island of Kauai in 1988. It was identified by the RTI and has been named "waimea." Three hundred twenty-four cases had either a definitive or presumptively identified infecting serogroup. Again, Icterohaemorrhagiae was the most common serogroup identified (52%), followed by Australis (21%) (Table 8).

TABLE 4
Multivariate analysis for confirmed cases of leptospirosis, State of Hawaii, by age-group, island of exposure, and ethnicity

Independent variable	Odds ratio	Likelihood ratio 95% confidence limits	*P*
Age group (years)*			
0–9	0.11	0.03, 0.29	< 0.0001
10–19	0.66	0.35, 1.19	0.17
20–29	1.41	0.87, 2.29	0.17
30–39	1.0 (Reference group)		
40–49	1.64	1.04, 2.61	0.03
50–59	0.84	0.42, 1.58	0.60
60–69	0.46	0.18, 0.98	0.04
70–79	0.40	0.11, 1.03	0.06
Island of exposure†			
Oahu	1.0 (Reference group)		
Hawaii	17.30	11.23, 27.50	< 0.0001
Kauai	27.61	17.27, 45.09	< 0.0001
Ethnicity‡			
Caucasian	1.0 (Reference group)		
Hawaiian/ part Hawaiian	0.78	0.50, 1.18	0.25
Japanese	0.50	0.31, 0.78	0.002
Filipino	0.23	0.11, 0.44	< 0.0001

* Adjusted for island of exposure and ethnicity.
† Adjusted for age group and ethnicity.
‡ Adjusted for age group and island of exposure.

An analysis of temporal trends revealed a statistically significant decrease in the proportion of cases attributed to serogroup Icterohaemorrhagiae (χ^2 for linear trend = 7.9, P = 0.005) and a statistically significant increase in the proportion of cases attributed to serogroup Australis (χ^2 for linear trend = 29.4, $P < 0.001$). An analysis of temporal trends by island revealed that the island of Kauai demonstrated the most pronounced decrease in the proportion of infections due to serogroup Icterohaemorrhagiae (χ^2 for linear trend = 12.4, $P < 0.001$) and increase in the proportion of infections due to serogroup Australis (χ^2 for linear trend = 20.7, $P <$ 0.001). The island of Hawaii demonstrated a significant in-

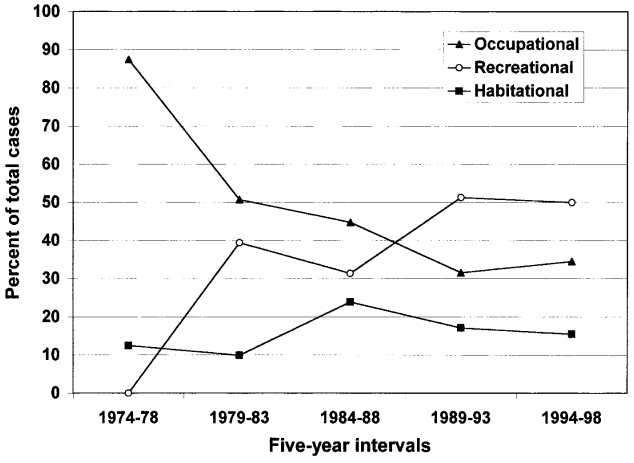

FIGURE 4. Trends in exposure classification for 335 confirmed leptospirosis cases, State of Hawaii, 1974–1998.

TABLE 5

Source of exposure by exposure classification for 335 confirmed leptospirosis cases, State of Hawaii, 1974–1998

Occupational (n = 137)
Agriculture–Animal related: Dairy farmer (5); Rancher (3); Swine farmer (3)
Agriculture–Non-Animal related: Taro farming (34); Farming, nonspecific (26); Gardener (7); Nursery worker (6); Clearing fields/removing foliage (5); Sugar worker (3); Papaya farmer (3); Banana farmer (2); Watercress farmer (2); Park ranger/forester (2); Camp caretaker (1); Potato farmer (1); Coffee farmer (1); Macadamia nut farmer (1); Lotus farmer (1)
Other animal related: Abattoir (2); Veterinarian (2); Raising animals (rabbits/birds) (2); Zoologist (1); Vector control (rat trapping) (1)
Military (2)
Scientist: Student on field trip (2); Biologist (1)
Construction work (4)
Tour guides (hiking and river) (3)
Aquaculture/fishing (9)
Waste management/sewerage (2)
Recreational (n = 143)*
Swimming (84)
Hiking/camping (27)
Prawning (21)
Hunting (14)
Fishing (10)
Surfing/body boarding in river (5)
Crabbing (2)
Canoeing/kayaking (2)
Playing with animals (2)
Cross-country running (1); Mud sliding (1); Waterskiing on river (1)
Habitational (exposed around the home) (n = 55)*
Gardening/yardwork (23)
Dogs (18)
Drinking catchment water (17)
Rats/mice (9)
Mud/water (including streams) around home (9)
Pigs (4)

*Sum of component activities are greater than total number of cases for exposure classification category since one case may have experienced greater than one exposure.

crease in proportion of infections due to serogroup Australis (χ^2 for linear trend = 9.1, $P = 0.003$); the trend in infections due to serogroup Icterohaemorrhagiae has been decreasing but has not reached statistical significance. Serogroup Icterohaemorrhagiae has remained steady as the predominant serogroup on the island of Oahu.

TABLE 6

Laboratory-confirmed leptospirosis outbreaks, State of Hawaii, 1974–1998

Year	Island	Number of cases	Exposure	Circumstances
1975	Hawaii	2	Occupational	Taro farming
1979	Oahu	2	Occupational	Dairy farming
1986	Oahu	2	Recreational	Swimming
1987	Kauai	8	Recreational	Swimming[37]
1992	Hawaii	3	Occupational	Ginger farming
1992	Oahu	2	Recreational	Swimming[80]

DISCUSSION

Annual leptospirosis incidence rates in the U.S. varied from 0.02 to 0.05 per 100,000 from 1974 to 1994.[10–30] The mean annual rate of 1.29 per 100,000 for Hawaii during the period 1974 to 1998 is approximately 30 times higher than that reported nationally. This difference is actually an underestimation, since the national statistics included probable and suspect cases (in addition to confirmed cases) in their total. If one includes all reported cases in Hawaii during this 25-year period, the mean annual rate more than doubles to 2.76 per 100,000. The tropical climate in Hawaii, large areas of high rainfall, large number of mammalian reservoirs, popularity of freshwater-related recreational activities, along with the attention focused on disease detection and identification, all contribute to the higher reported case rates observed in Hawaii. Surveys of rats, mice, and mongooses on the island of Hawaii[38–40] and Oahu[41] have documented the enzootic presence of leptospirosis in both urban and rural settings. Prevalence among Norway rats (*Rattus norvegicus*) has ranged from 33% to 61%. Other animal studies in the state have also documented a high prevalence of leptospiral infection among a number of different species, including cattle, dogs, and swine.[42]

The annual reported leptospirosis incidence rates demonstrated a significant increase over this 25-year period (Figure 1). However, the most likely explanation for this trend is related to public health interest and ongoing prevention/education programs, resulting in increasing awareness and recognition of leptospirosis rather than a true increase in disease occurrence. Three fatalities linked to leptospirosis in 1978 (one confirmed, one probable, and one suspect case) led to a more focused surveillance effort and a concurrent increase

TABLE 7

Leptospira culture isolates (by serogroup*), State of Hawaii, 1974–1998

Serogroup†	1979–1983	1984–1988	1989–1993	1994–1998	Total
Australis (H, K, O)	0	4	5	10	19
Ballum (H)	0	4	1	0	5
Bataviae (K, M, O)	0	2	2	1	5
Icterohemorrhagiae (H, K, N, O)	10	11	13	9	43
Pomona (O)	1	0	0	0	1
Sejroe (H, O)	0	1	0	1	2
Identification pending	0	0	0	6	6
Total	11	22	21	27	81

* Because the Centers for Disease Control and Prevention has been serogrouping (and not serotyping) leptospiral culture isolates since 1991, only serogroup identification is provided; however the following serovars were identified, 1974–1991: serovars *australis* and *bangkok,* serogroup Australis; serovar *ballum,* serogroup Ballum; serovars *djatzi, bataviae,* and *waimea,* serogroup Bataviae; serovars *icterohaemorrhagiae, copenhageni, bog-vere,* and *tonkini,* serogroup Icterohaemorrhagiae; serovar *pomona,* serogroup Pomona; serovar *hardjo-bovis,* serogroup Sejroe.

†H = island of Hawaii; K = island of Kauai; O = island of Oahu; M = island of Maui; N = island of Niihau.

TABLE 8

Leptospira serogroups for 324 confirmed cases, State of Hawaii 1974−1998, as shown by isolate or presumptively (by microscopic agglutination test [MAT])*

Serogroup	1974–1978	1979–1983	1984–1988	1989–1993	1994–1998	Total
Andamana	0	1	0	0	0	1
Australis†	1	5	10	11	40	67
Autumnalis	0	5	2	0	1	8
Ballum†	0	4	8	7	3	22
Bataviae†	0	0	2	4	1	7
Canicola‡	0	7	3	4	4	18
Cynopteri	0	0	0	1	0	1
Djasiman	0	1	0	0	0	1
Hebdomadis	0	1	0	0	0	1
Icterohemorrhagiae†	7	44	37	46	36	170
Mini	0	0	0	0	6	6
Pomona†	0	2	0	0	0	2
Pyrogenes	0	2	1	0	1	4
Sejroe†	1	4	4	0	4	13
Tarassovi	0	0	2	0	1	3
Total	9	76	69	73	97	324

* Serogroups identified presumptively by MAT may reflect cross-reactivity.
†Isolated in the State of Hawaii from animals and humans.
‡Isolated in the State of Hawaii from animals but not humans.

in reported cases. The peak in 1988 reflects the impact of an active surveillance study on the islands of Hawaii and Kauai.[43] The peak in 1992 may be related to the publicity surrounding two fatalities in 1991 (one confirmed and one probable case). Recent increases in case reports may be the result of an ongoing effort by the DOH to increase the collection of convalescent phase sera from suspect cases who have had acute-phase sera specimens already drawn by actively reminding clinicians of the need to assess changes in the titers of paired sera in order to confirm the diagnosis.

It is very likely that the number of reported cases both in Hawaii and nationally reflect an underestimation of true disease occurrence, since less severe cases may go unrecognized and thus undetected. Studies from several large U.S. cities have documented serologic evidence of unrecognized past leptospiral infections in a substantial number of urban residents. The prevalence of antibody to *Leptospira* (defined as having sera reactive at a minimum titer of 1:200 by IgG ELISA) was 16% (185 of 1,150) among sexually transmitted disease clinic patients in Baltimore,[44] while 31% (39 of 124) of children undergoing lead exposure examinations in Detroit showed single MAT titers $\geq$ 1:10.[45] Surveillance of pediatric hospital admissions for leptospirosis during a four-year period in St. Louis, Missouri detected 25 children with serologic evidence of past or current infection (stable MAT titer $\geq$ 1:100 in two or more serum specimens), in addition to nine confirmed cases.[46] An active surveillance study in Hawaii (1988–1989) led to a five-fold increase in case detection compared with case reports based on passive surveillance (case definition: minimum MAT titer = 1:200, culture isolation, or demonstration of fluorescent antibody tissue staining on autopsy).[43] Animal trapping studies have also documented a high prevalence ($>$ 50%) of infected rats in urban Baltimore (19 of 21 positive by polymerase chain reaction [PCR])[47] and Detroit (221 of 373 culture positive).[48] The ubiquitous nature of the infection has led one researcher to question whether the current categorization of leptospirosis as a re-emerging disease is appropriate; instead, the term re-discovered has been suggested as an alternative.[49]

Additional challenges to detecting/confirming cases of leptospirosis include problems associated with isolating the organism and serologic testing. Culture isolation requires special laboratory techniques and media, and may take several weeks. Although most positive cultures are apparent within the first two weeks, the CDC recommends holding cultures for four months before calling them negative.[32] In Hawaii, the DOH holds cultures for six weeks. The MAT is currently considered the reference serologic test for leptospirosis infection. However, the methodologic complexity of the MAT limits its use. Only a few laboratories, world-wide, are capable of providing *Leptospira* diagnostics.[32] The reference laboratory for human leptospirosis in the United States is the World Health Organization/Food and Agricultural Organization Collaborating Center for Reference and Research on Leptospirosis at the CDC in Atlanta, Georgia.[32] In addition, since MAT confirmation requires demonstration of a four-fold titer increase in paired acute- and convalescent-phase sera, numerous factors impede collection of the convalescent-phase sera, even when the diagnosis of leptospirosis has been entertained. Sixty-two of 180 probable cases (34%) and 40 of 176 suspect cases (23%) had only single acute serum specimens submitted for MAT evaluation, excluding the possibility of adequately assessing MAT confirmation. The DOH currently sends letters requesting a convalescent-phase serum specimen to all physicians submitting an acute-phase serum specimen for leptospirosis testing.

The IHA has been available for leptospirosis screening purposes in the U.S. Although published reports have shown the IHA to have high sensitivity and specificity,[50] experience in Hawaii has demonstrated suboptimal sensitivity, limiting its usefulness as a diagnostic test.[51] Polymerase chain reaction assays using DNA primers from highly conserved regions of pathogenic *Leptospira* species have demonstrated the ability to recognize the majority of pathogenic *Leptospira* species.[52] These assays have also been shown to be more rapid than culture isolation, with high sensitivity when used in the early leptospiremic stage of the disease.[53,54] However, as the disease progresses from the leptospiremic stage

to the immune stage, with increasing leptospiral antibody titers, the ability of the PCR assay to detect infection decreases dramatically.[55,56] In addition, PCR assays require special resources, skills, and equipment. In Europe, Australia, and other regions outside the United States, IgM detection assays, including IgM ELISAs, have been available for the rapid, presumptive diagnosis of leptospirosis.[49,51] The U.S. Food and Drug Administration has recently approved the first IgM Dot-ELISA leptospirosis test for use in the United States.[57]

A male predominance for this disease has been consistently reported.[58–61] This is most likely related to a male predominance in high-risk outdoor exposure activities both occupationally and recreationally.

The low reported occurrence in children less than 10 years old has also been previously noted.[58,60–62] Likely explanations are not that there is a lower occurrence of cases in this age group, but rather the majority of cases are not recognized or not tested, and thus go undiagnosed. The nonspecific symptoms of leptospirosis are often attributed to a viral illness.[46] Population-based leptospirosis serologic surveys have documented evidence of subclinical infections in children,[63,64] leading some researchers to question whether children manifest milder symptoms than adults.[65] The predominance of cases in the 20–50-year-old age group is well recognized and is felt to be related to increased environmental exposures.[66]

Although the overall temporal trend for the state was one of decreasing exposures related to occupational activities and increasing exposures related to recreational activities, an analysis of trends in exposure classification by island revealed no apparent trends on the island of Hawaii. Hawaii, which is a rural agricultural island, was the only island with the majority of cases being related to occupational exposures. In contrast, the island with the highest case rates, Kauai, demonstrated a statistically significant increase in the proportion of exposures related to recreational activities (χ^2 for linear trend = 5.3, $P = 0.02$). While the trend in occupational exposures decreased, it did not reach statistical significance ($P = 0.051$). The two most commonly reported exposure locations on Kauai were linked to recreational exposures: the Hanalei area including the Na Pali Coast with a popular hiking trail, and the Waimea River recreational area. Analysis of temporal trends on Oahu revealed a decrease in occupational exposures ($P = 0.06$) and an increase in recreational exposures over time ($P = 0.07$), but neither reached statistical significance.

The statewide trends in exposure related activities mirror the dramatic changes in the state's economic focus, with a downsizing of the agricultural sector, most notably in the sugar and pineapple industries, and a concurrent increased emphasis on tourism. The Hamakua District on the island of Hawaii, the center for the state's sugar industry, had the highest leptospirosis rates in the State in the 1960s;[42] however, this region has lost 10% of its population each decade since 1970 due to the cutback and eventual closure of sugar operations.[67]

The high percentage of reported dog exposures in this series is not unexpected. Domestic pets in general[60] and dogs specifically[59] have been listed as the predominant animal source of human exposure in previously published national case series. Dogs are a well-recognized reservoir for *Leptospira*.[68] Alternatively, confounding by agricultural exposures or high prevalence of dog ownership might also explain this finding.

The majority of cases statewide are associated with exposures in rural settings, with the more rural islands having higher rates of leptospirosis. Kauai, with 44.8% of its population residing in rural areas, has the highest leptospirosis rate followed by the island of Hawaii (39.2% rural). The islands of Maui (21.9% rural) and Oahu (3.6% rural) have lower rates.[69] The high case rate on Kauai may also be related to rainfall. Kauai has the highest annual rainfall of the Hawaiian islands, and is home of the wettest spot on earth, Waialeale, with 450 inches of rain per year.[70]

The majority of cases are also located on the wetter, windward, northeast sides of each island. These factors may help to explain the observed lower rates from the island of Maui, where approximately 80% of the island's population reside on the leeward side of the island, which has less rainfall and is more urban. The rural, windward, east side (Hana) of the island is geographically isolated with limited access via a single, narrow two-lane serpentine highway. Limited animal trapping studies done on Maui have demonstrated serologic evidence of leptospirosis in both mongooses and rodents,[42] although *Leptospira* isolates from these animals have been rare (DOH, unpublished data). In addition, the Norway rat (*Rattus norvegicus*), which has been shown to be the animal vector in Hawaii with the highest rate of infection in past published reports,[38,41] has been infrequently recovered during rodent trapping efforts on Maui.[42] An earlier state-wide seroprevalence survey of blood donors revealed the lowest rates of infection from blood donors on Maui (DOH, unpublished data).

Differences in the distribution of cases by ethnic group are most likely explained by ethnic differences in exposure related activities. The lower rates for Japanese and Filipinos in this series may in part reflect the paucity of ethnic data collected during the first 14 years of this 25-year series, during which time occupational exposures predominated, as a substantial proportion of agricultural workers were of Japanese and Filipino ethnicity. However, it is noteworthy that an earlier leptospirosis case series from Hawaii found that being of Filipino ethnicity was also noted to be protective. Of 37 persons with leptospirosis admitted to the Olaa Hospital on the Island of Hawaii between 1941 and 1943, 35 (95%) were male day laborers of the Olaa Sugar Company. The ethnic-specific incidence rates were lowest among Filipino workers: four cases among 755 workers (5.3 per 1,000) compared with 30 cases among 659 Japanese day laborers (45.5 per 1,000). The investigator attributed this discordance in distribution to the older age distribution of the Filipino workers (mean age = 41 years) compared with the Japanese workers (mean age = 19 year), hypothesizing that Filipino workers may be immune to leptospirosis due to past exposures.[71] However, in the current series, being of Japanese or Filipino ethnicity remained independently associated with a lower risk for leptospirosis, compared with persons of Caucasian ethnicity, even after adjustment for age and island of exposure. The explanation for the observed ethnic differences may be multifactorial and remains to be fully elucidated.

Seasonal trends in leptospirosis have been well recognized

in the United States, with peak occurrence described during the months July–October.[66] A definite predominance in disease occurrence is present in Hawaii, from July to December (Figure 2), and even when month of onset is assessed for each exposure class (occupational, recreational, and habitational), the peak occurrence remains consistently high during the latter six months of the year. Since rainfall in Hawaii is generally highest in the winter months and lowest in summer,[70] the seasonal variation in case occurrence is more likely related to increased environmental exposures in the summer and fall when the weather is warmest than to rainfall.

This large case series is unique in its presentation of only confirmed cases meeting specific laboratory diagnostic criteria.[32,33] The majority of previously published case series either included all case reports in their analysis, including those without laboratory confirmation,[59,60] or used a variety of less specific case definitions for the purposes of confirmation, including a single MAT titer $\geq$ 1:100,[58,62] any increase or decrease in titer against one or more serotypes,[58] MAT seroconversion (a negative result in the first serum sample and a titer $\geq$ 1:100 in the second sample),[72,73] an MAT titer $>$ 1:200 with an increase/decrease in a subsequent serum specimen,[74] a single MAT titer $\geq$ 1:400,[72] or a single MAT titer $>$ 1:400.[75] It is important to differentiate confirmed from probable, presumptive, or suspect cases to optimally characterize leptospirosis epidemiologically. The use of consistent diagnostic criteria is also necessary to allow for valid comparisons between different cases series. This case series reflects the majority of recognized leptospirosis within the U.S. from 1974 to 1998, and is the first large U.S. case series/surveillance report to be published since that of Martone and Kaufmann in 1979.[60] It is important to recognize that the 353 cases reported in this series reflect only cases exposed and diagnosed in the State of Hawaii. An estimated 6.7 million tourists visited Hawaii in 1998.[76] Since the 7–12-day incubation period for leptospirosis[77,78] exceeds the median length of stay for a tourist (7 days),[76] there are no doubt many more additional unrecognized cases, related to exposures in Hawaii, which occur after a tourist returns to his or her home.[79] The increased recognition of leptospirosis as the cause of serious illness, and recent categorization of leptospirosis as a re-emerging infectious disease may justify reconsideration of the decision to exclude it from the list of national notifiable diseases.

Acknowledgments: Grateful acknowledgements are given to the following individuals: Harry Domen, Henry Higa, Mitsuto Sugi, Chester Wakida, and Sally Jo Manea from the Hawaii State Department of Health (DOH) for assistance with case investigation and laboratory support; Henri Minette, Robert Worth, and Richard Vogt (DOH) for expert consultation and epidemiologic assistance; Tammy Tom (DOH) for expert technical assistance; Arnold Kaufmann, Catherine Sulzer, Faye Rogers, Sandra Bragg, and Robbin Weyant (U.S. Centers for Disease Control and Prevention) for laboratory support; Wiepko Terpstra, Hans Korver, and Rudy Hartskeerl (Royal Tropical Institute, Amsterdam, the Netherlands) for laboratory support; Linda Odello (University of Hawaii School of Public Health) for data entry and technical support; F. DeWolfe Miller and John S. Grove (University of Hawaii John A. Burns School of Medicine) for expert statistical and epidemiologic consultation and support; and Virginia M. Tanji (University of Hawaii John A. Burns School of Medicine) for reference assistance.

Financial support: Part of this research was supported by the State of Hawaii Department of Health through a grant administered by the Research Corporation of the University of Hawaii.

Authors' addresses: Alan R. Katz, Department of Public Health Sciences and Epidemiology, John A. Burns School of Medicine, University of Hawaii, Biomedical Sciences Building, Room D104-K, 1960 East-West Road, Honolulu, HI 96822. Vernon E. Ansdell, Kaiser Permanente Medical Care Program, Koolau Clinic, 45–602 Kamehameha Highway, Kaneohe, HI 96744. Paul V. Effler and David M. Sasaki, Hawaii State Department of Health, Epidemiology Branch, PO Box 3378, Honolulu, HI 96801. Charles R. Middleton, 615 Lawelawe Street, Honolulu, HI 96821.

REFERENCES

1. World Health Organization, 1999. Leptospirosis worldwide, 1999. *Wkly Epidemiol Rec 74:* 237–242.
2. Meslin F-X, 1997. Global aspects of emerging and potential zoonoses: a WHO perspective. *Emerg Infect Dis 3:* 223–228.
3. Trevejo RT, Rigau-Pérez JG, Ashford DA, McClure EM, Jarquín-González C, Amador JJ, de los Reyes JO, Gonzalez A, Zaki SR, Shieh W-J, McLean RG, Nasci RS, Weyant RS, Bolin CA, Bragg SL, Perkins BA, Spiegel RA, 1998. Epidemic leptospirosis associated with pulmonary hemorrhage-Nicaragua, 1995. *J Infect Dis 178:* 1457–1463.
4. Centers for Disease Control and Prevention, 1997. Outbreak of leptospirosis among white-water rafters-Costa Rica, 1996. *MMWR Morb Mortal Wkly Rep 46:* 577–579.
5. Ko AI, Reis MG, Ribeiro Dourado CM, Johnson WD Jr, Riley LW, Salvador Leptospirosis Study Group, 1999. Urban epidemic of severe leptospirosis in Brazil. *Lancet 354:* 820–825.
6. World Health Organization, 2000. Leptospirosis, India. *Wkly Epidemiol Rec 75:* 217–223.
7. Centers for Disease Control and Prevention, 1998. Update: leptospirosis and unexplained acute febrile illness among athletes participating in triathlons–Illinois and Wisconsin, 1998. *MMWR Morb Mortal Wkly Rep 47:* 673–676.
8. Centers for Disease Control and Prevention, 2000. Public health dispatch: outbreak of acute febrile illness among participants in EcoChallenge Sabah 2000 Malaysia, 2000. *MMWR Morb Mortal Wkly Rep 49:* 816–817.
9. World Health Organization, 2000. Outbreak news. *Wkly Epidemiol Rec 75:* 305, 313.
10. Center for Disease Control, 1975. Reported morbidity and mortality in the United States, 1974. Annual supplement, 1974. *MMWR Morb Mortal Wkly Rep 23:* 7, 10.
11. Center for Disease Control, 1976. Reported morbidity and mortality in the United States, 1975. Annual supplement summary, 1975. *MMWR Morb Mortal Wkly Rep 24:* 7, 10.
12. Center for Disease Control, 1977. Reported morbidity and mortality in the United States, 1976. Annual summary, 1976. *MMWR Morb Mortal Wkly Rep 25:* 8, 11.
13. Center for Disease Control, 1978. Reported morbidity and mortality in the United States. Annual summary, 1977. *MMWR Morb Mortal Wkly Rep 26:* 9, 12.
14. Center for Disease Control, 1979. Reported morbidity and mortality in the United States. Annual summary, 1978. *MMWR Morb Mortal Wkly Rep 27:* 8, 10.
15. Center for Disease Control, 1980. Reported morbidity and mortality in the United States. Annual summary, 1979. *MMWR Morb Mortal Wkly Rep 28:* 4, 6.
16. Centers for Disease Control, 1981. Reported morbidity and mortality in the United States. Annual summary, 1980. *MMWR Morb Mortal Wkly Rep 29:* 4, 6.
17. Centers for Disease Control, 1982. Reported morbidity and mortality in the United States. Annual summary, 1981. *MMWR Morb Mortal Wkly Rep 30:* 4, 6.
18. Centers for Disease Control, 1983. Reported morbidity and mortality in the United States. Annual summary, 1982. *MMWR Morb Mortal Wkly Rep 31:* 4, 6.
19. Centers for Disease Control, 1984. Reported morbidity and mortality in the United States. Annual summary, 1983. *MMWR Morb Mortal Wkly Rep 32:* 4, 6.
20. Centers for Disease Control, 1986. Reported morbidity and mor-

tality in the United States. Annual summary, 1984. *MMWR Morb Mortal Wkly Rep 33:* 4, 6.
21. Centers for Disease Control, 1985. Summary of notifiable diseases, United States, 1985. *MMWR Morb Mortal Wkly Rep 34:* 4, 6.
22. Centers for Disease Control, 1986. Summary of notifiable diseases, United States, 1986. *MMWR Morb Mortal Wkly Rep 35:* 4, 6.
23. Centers for Disease Control, 1987. Summary of notifiable diseases, United States, 1987. *MMWR Morb Mortal Wkly Rep 36:* 4, 6.
24. Centers for Disease Control, 1988. Summary of notifiable diseases, United States, 1988. *MMWR Morb Mortal Wkly Rep 37:* 4, 6.
25. Centers for Disease Control, 1989. Summary of notifiable diseases, United States, 1989. *MMWR Morb Mortal Wkly Rep 38:* 4, 6.
26. Centers for Disease Control, 1990. Summary of notifiable diseases, United States, 1990. *MMWR Morb Mortal Wkly Rep 39:* 4, 6.
27. Centers for Disease Control, 1991. Summary of notifiable diseases, United States, 1991. *MMWR Morb Mortal Wkly Rep 40:* 4, 6.
28. Centers for Disease Control and Prevention, 1992. Summary of notifiable diseases, United States, 1992. *MMWR Morb Mortal Wkly Rep 41:* 4, 6.
29. Centers for Disease Control and Prevention, 1993. Summary of notifiable diseases, United States, 1993. *MMWR Morb Mortal Wkly Rep 42:* 4, 6.
30. Centers for Disease Control and Prevention, 1994. Summary of notifiable diseases, United States, 1994. *MMWR Morb Mortal Wkly Rep 43:* 4, 6.
31. Centers for Disease Control and Prevention, 1995. Summary of notifiable diseases, United States, 1995. *MMWR Morb Mortal Wkly Rep 44:* 1–87.
32. Weyant RS, Bragg SL, Kaufmann AF, 1999. Leptospira and leptonema. Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, eds. *Manual of Clinical Microbiology.* Seventh edition. Washington, DC: American Society for Microbiology, 739–745.
33. Faine S, 1998. Leptospirosis. Hausler WJ Jr, Sussman M, eds. Collier L, Balows A, Sussman M, eds. *Topley & Wilson's Microbiology and Microbial Infections.* Ninth edition. Volume 3. *Bacterial Infections.* London: Arnold, 849–869.
34. Centers for Disease Control and Prevention, 1997. Case definitions for infectious conditions under public health surveillance. *MMWR Morb Mortal Wkly Rep 46:* 49.
35. Sulzer CR, Jones WL, 1978. *Leptospirosis: Methods in Laboratory Diagnosis.* Revised edition. Atlanta, GA: U.S. Department of Health, Education, and Welfare, Public Health Service. Publication No.: CDC 78–8275.
36. U.S. Department of Commerce, Economics and Statistics Administration, Bureau of the Census, 1990. *1990 Census of population. General population characteristics. Hawaii.* Washington, DC: U.S. Dept. of Commerce; Report No.: 1990 CP-1–13.
37. Katz AR, Manea SJ, Sasaki DM, 1991. Leptospirosis on Kauai: investigation of a common source waterborne outbreak. *Am J Public Health 81:* 1310–1312.
38. Minette HP, 1964. Leptospirosis in rodents and mongooses on the island of Hawaii. *Am J Trop Med Hyg 13:* 826–832.
39. Shimizu M, 1984. Environmental and biological determinants for the prevalence of leptospirosis among wild small mammal hosts, Island of Hawaii. *Int J Zoon 11:* 173–188.
40. Tomich PQ, 1980. Studies of leptospirosis in natural host populations, 1. Small mammals of Waipio Valley, Island of Hawaii. *Pacific Science 33:* 257–259.
41. Higa HH, Fujinaka IT, 1976. Prevalence of rodent and mongoose leptospirosis on the island of Oahu. *Public Health Rep 91:* 171–177.
42. Anderson BS, Minette HP, 1986. Leptospirosis in Hawaii: shifting trends in exposure, 1907–1984. *Int J Zoon 13:* 76–88.
43. Sasaki DM, Pang L, Minette HP, Wakida CK, Fujimoto WJ, Manea SJ, Kunioka R, Middleton CR, 1993. Active surveillance and risk factors for leptospirosis in Hawaii. *Am J Trop Med Hyg 48:* 35–43.
44. Childs JE, Schwartz BS, Ksiazek TG, Graham RR, LeDuc JW, Glass GE, 1992. Risk factors associated with antibodies to leptospires in inner-city residents of Baltimore: a protective role for cats. *Am J Public Health 82:* 597–599.
45. Demers RY, Thiermann A, Demers P, Frank R, 1983. Exposure to *Leptospira icterohemorrhagiae* in inner-city and suburban children: a serologic comparison. *J Fam Pract 17:* 1007–1011.
46. Wong ML, Kaplan S, Dunkle LM, Stechenberg BW, Feigin RD, 1977. Leptospirosis: a childhood disease. *J Pediatr 90:* 532–537.
47. Vinetz JM, Glass GE, Flexner CE, Mueller P, Kaslow DC, 1996. Sporadic urban leptospirosis. *Ann Intern Med 125:* 794–798.
48. Thiermann AB, 1977. Incidence of leptospirosis in the Detroit rat population. *Am J Trop Med Hyg 26:* 970–974.
49. Levett PN, 1999. Leptospirosis: re-emerging or re-discovered disease? *J Med Microbiol 48:* 417–418.
50. Levett PN, Whittington CU, 1998. Evaluation of the indirect hemagglutination assay for diagnosis of acute leptospirosis. *J Clin Microbiol 36:* 11–14.
51. Effler PV, Domen HY, Bragg SL, Aye T, Sasaki DM, 2000. Evaluation of the indirect hemagglutination assay for diagnosis of acute leptospirosis in Hawaii. *J Clin Microbiol 38:* 1081–1084.
52. Letocart M, Baranton G, Perolat P, 1997. Rapid identification of pathogenic *Leptospira* species (*Leptospira interrogans, L. borgpetersenii,* and *L. kirschneri*) with species-specific DNA probes produced by arbitrarily primed PCR. *J Clin Microbiol 35:* 248–253.
53. Bal AE, Gravekamp C, Hartskeerl RA, De Meza-Brewster J, Korver H, Terpstra WJ, 1994. Detection of leptospires in urine by PCR for early diagnosis of leptospirosis. *J Clin Microbiol 32:* 1894–1898.
54. Brown PD, Gravekamp C, Carrington DG, van de Kemp H, Hartskeerl RA, Edwards CN Everard COR, Terpstra WJ, Levett PN, 1995. Evaluation of the polymerase chain reaction for early diagnosis of leptospirosis. *J Med Microbiol 43:* 110–114.
55. Merien F, Baranton G, Perolat P, 1995. Comparison of polymerase chain reaction with microagglutination test and culture for diagnosis of leptospirosis. *J Infect Dis 172:* 281–285.
56. Yersin C, Bovet P, Smits HL, Perolat P, 1999. Field evaluation of a one-step dipstick assay for the diagnosis of human leptospirosis in the Seychelles. *Trop Med Int Health 4:* 38–45.
57. U.S. Food and Drug Administration. Center for Devices and Radiologic Health. 510(k)s final decisions rendered for November 2000. Device: PanBio InDx Dip-S-Ticks Leptospirosis Test. 501(k) No. K002024. Summary of safety and effectiveness data. Available from URL: http://www.fda.gov/cdrh/501k/sumnov00.html.
58. Heath CW Jr, Alexander AD, Galton MM, 1965. Leptospirosis in the United States: analysis of 483 cases in man, 1949–1961. *N Engl J Med 273:* 857–864, 915–922.
59. Kaufmann AF, 1976. Epidemiologic trends of leptospirosis in the United States, 1965–1974. Johnson RC, ed. *The Biology of Parasitic Spirochetes.* New York: Academic Press, 177–189.
60. Martone WJ, Kaufmann AF, 1979. From the Center for Disease Control: Leptospirosis in humans in the United States, 1974–1978. *J Infect Dis 140:* 1020–1022.
61. Everard COR, Edwards CN, Everard JD, Carrington DG, 1995. A twelve-year study of leptospirosis on Barbados. *Eur J Epidemiol 11:* 311–320.
62. Perrocheau A, Perolat P, 1997. Epidemiology of leptospirosis in New Caledonia (South Pacific): a one-year survey. *Eur J Epidemiol 13:* 161–167.
63. Ratnam S, Sundararaj T, Subramanian S, 1983. Serological evidence of leptospirosis in a human population following an outbreak of the disease in cattle. *Trans R Soc Trop Med Hyg 77:* 94–98.
64. Everard COR, Fraser-Chanpong GM, 1979. Serological evi-

dence of leptospirosis in Caribbean schoolchildren. *Trans R Soc Trop Med Hyg 73:* 591–593.
65. Everard COR, Edwards CN, Webb GB, White HSC, Nicholson GD, 1984. The prevalence of severe leptospirosis among humans on Barbados. *Trans R Soc Trop Med Hyg 78:* 596–603.
66. Faine S, 1998. Leptospirosis. Evans AS, Brachman PS, eds. *Bacterial Infections of Humans: Epidemiology and Control.* Third edition. New York: Plenum Publishing, 395–420.
67. Schmitt RC, 1998. Population. Juvik SP, Juvik JO, eds. *Atlas of Hawaii.* Third edition. Honolulu: University of Hawaii Press, 183–197.
68. Torten M, Marshall RB, 1994. Leptospirosis. Beran GW, Steele JH, eds. *Handbook of Zoonoses.* Second edition. *Section A: Bacterial, Rickettsial, Chlamydial, and Mycotic.* Boca Raton, FL: CRC Press, 245–264.
69. U.S. Department of Commerce, Economics and Statistics Administration, Bureau of the Census, 1993. *1990 Census of Population and Housing. Population and Housing Unit Counts, Hawaii.* Washington, DC: U.S. Dept. of Commerce; Report No.: 1990 CPH-2–13.
70. Giambelluca TW, Schroeder TA, 1998. Climate. Juvik SP, Juvik JO, eds. *Atlas of Hawaii.* Third edition. Honolulu: University of Hawaii Press, 49–59.
71. Patterson HM, 1944. Weil's disease. A report of thirty-seven cases. *Hawaii Med J 3:* 213–221.
72. Merien F, Perolat P, 1996. Public health importance of human leptospirosis in the South Pacific: a five-year study in New Caledonia. *Am J Trop Med Hyg 55:* 174–178.
73. Yersin C, Bovet P, Mérien F, Wong T, Panowsky J, Perolat P, 1998. Human leptospirosis in the Seychelles (Indian Ocean): a population-based study. *Am J Trop Med Hyg 59:* 933–940.
74. Kuriakose M, Eapen CK, Paul R, 1997. Leptospirosis in Kolenchery, Kerala, India: epidemiology, prevalent local serogroups and serovars and a new serovar. *Eur J Epidemiol 13:* 691–697.
75. Shenberg E, Gerichter CB, Lindenbaum I, 1982. Leptospirosis in man, Israel, 1970–1979. *Am J Epidemiol 115:* 352–358.
76. State of Hawaii Department of Business, Economic Development and Tourism, 1998. *The State of Hawaii Data Book: 1998, A Statistical Abstract.* Honolulu: State of Hawaii.
77. Faine S, Adler B, Bolin C, Perolat P, 1999. *Leptospira and Leptospirosis.* Second edition. Melbourne: MediSci.
78. Farr RW, 1995. Leptospirosis. *Clin Infect Dis 21:* 1–8.
79. van Crevel R, Speelman P, Gravekamp C, Terpstra WJ, 1994. Leptospirosis in travelers. *Clin Infect Dis 19:* 132–134.
80. Katz AR, Sasaki DM, Mumm AH, Escamilla J, Middleton CR, Romero SE, 1997. Leptospirosis on Oahu: an outbreak among military personnel associated with recreational exposure. *Mil Med 162:* 101–104.