Travel-Related Leptospirosis in Israel: A Nationwide Study

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Abstract. Leptospirosis is re-emerging in developed countries as a travel-related infection. In this nationwide study of travel-related leptospirosis in Israel, all cases diagnosed at the Central Reference Laboratory for Leptospirosis, during 2002–2008 were retrospectively reviewed and only travel-related cases were included. During the study years, 20 (42%) of 48 leptospirosis cases in Israel were travel-related. Exposure occurred in Southeast Asia in 15 (75%) of 20 cases. The estimated yearly incidence of travel-related leptospirosis was 1.78/100,000 travelers compared with an incidence of endemic cases of 0.06/100,000 inhabitants (risk ratio = 29.6, 95% confidence interval = 16.7–52.4). Most patients (89%) were infected during water-related activities. Severe disease was present in 10 (55%) of 18 patients; 7 of them were presumptively infected with the Icterohaemorrhagiae serogroup. Thus, travel-related leptospirosis is becoming increasingly important in the epidemiology of leptospirosis in Israel. Leptospirosis should be suspected in any traveler with undifferentiated febrile illness, especially when water exposure is reported.

INTRODUCTION

Leptospirosis is a zoonosis caused by infection with the pathogenic *Leptospira* species.¹ The disease occurs worldwide and has a wide spectrum of clinical manifestations, ranging from a mild self-limited febrile illness to severe multi-organ failure with high mortality rates.¹

Clinical data regarding leptospirosis among travelers is scarce. Most cases of travel-related leptospirosis previously described in the literature occurred in an epidemic setting among groups participating in water-related activities.^{2,3} There are several case reports of sporadic travel-related leptospirosis.^{4–6} However, there is only one previous report summarizing a case series of leptospirosis acquired during travel on a national level.⁷ In contrast with outbreak settings during which identification of related cases is relatively simple, the diagnosis of sporadic cases of leptospirosis in travelers requires a high level of suspicion.^{4,7,8}

There is no simple, widely available method of diagnosing leptospirosis during the acute illness. Because of its non-specific clinical presentation, many cases probably remain undiagnosed. Empiric treatment is the rule in the absence of a definitive diagnosis during the acute illness.

Previous studies reported a decrease in the incidence of endemic leptospirosis in Israel during the past 20 years.^{9,10} However, only one case of travel-related leptospirosis was reported in these previous reports. Leptospirosis is gaining special attention with the increase in adventure travel and water-related activities.^{8,11} In this nation-wide survey, we summarize the epidemiologic and clinical features of travel-related leptospirosis in Israel.

MATERIALS AND METHODS

In Israel, leptospirosis is a notifiable disease. All serologic investigations of patients with suspected leptospirosis are conducted by the Central Reference Laboratory for Leptospirosis in the Israel Institute for Biological Research in Ness Ziona.

The laboratory also serves as a reference center for the World Health Organization. *Leptospira* serologic investigation is performed using the microscopic agglutination test (MAT) method, in which antigens of 22 live *Leptospira* serovars are reacted with patient serum samples and agglutination is detected using darkfield microscopy (see Appendix 1 for a list of the serovars used⁹). Each serovar used in this method represents a common *Leptospira* serogroup. The method is extensively described elsewhere.^{1,12} It should be noted that the MAT can only presumptively identify infecting serogroups because of cross-reactivity and cross-agglutination.¹³

All records of the Central Reference Laboratory for Leptospirosis during 2002–2008 were retrospectively reviewed to identify cases of travel-related leptospirosis. Available patient files were reviewed and data obtained included demographic details, clinical and laboratory data, travel history, and possible mode of exposure (especially including water-related activities).

A confirmed case of leptospirosis was defined by one of the following features: 1) acute-phase serum MAT-determined antibody titer $\geq 1:200$ against any of the antigens, 2) an increase ≥ 4 times in MAT titer between acute-phase and convalescent-phase serum specimens, 3) isolation of *Leptospira* species from a clinical specimen, and 4) demonstration of *Leptospira* species in a clinical specimen by immunofluorescence.

Confirmed travel-related leptospirosis cases were defined as patients with symptoms and signs compatible with leptospirosis occurring less than 21 days after return from abroad, and the diagnosis was laboratory-confirmed as previously described.

The study was reviewed and approved by the Sheba Medical Center institutional review board. Fisher's exact test was used for categorical data and the Student *t*-test for continuous data. Statistical significance was set at $P < 0.05$.

RESULTS

During 2002–2008, 1,806 patients underwent laboratory evaluation for suspected leptospirosis at the Central Reference Laboratory (Figure 1). Of the patients evaluated, 33 (1.8%) were returned travelers. The total number of confirmed leptospirosis cases diagnosed during this period was 48, of which 20 (42%) were travel-related (Figure 1). The annual

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FIGURE 1. Flow chart of study of travel-related leptospirosis in Israel.

percentage of travel-related leptospirosis cases increased from 26% during 2002–2003 to 83% in the last year of the study (Figure 2). Detailed clinical data were available for 18 (90%) of the travelers. Based on the estimated yearly number of Israeli travelers to tropical countries of 160,000/year,¹⁴ the incidence of leptospirosis during 2002–2008 among this population is 1.78/100,000 travelers per year. During the same years, the estimated yearly incidence of endemic leptospirosis was 0.06/100,000 inhabitants. Thus, the risk ratio for acquiring leptospirosis during travel to tropical countries was 29.6 (95% confidence interval = 16.7–52.4).

The demographic and epidemiologic features characterizing our leptospirosis cases are summarized in Table 1. Most of the patients (18 of 20, 90%) were males and the mean $\pm$ SD patient age was 28 ± 9 years (range = 19–56 years). Exposure occurred in Southeast Asia in most cases (15 of 20, 75%). Participation in water-related activities was the probable mode of exposure in 89% of the patients. The mean $\pm$ SD incubation period was 11 ± 3 days (range = 5–18 days).

Diagnosis was made by MAT in all cases. In 17 (85%) of 20 cases, an increase in MAT titer ≥ 4 fold was demonstrated in paired serum specimens. In the other three cases (15%), the diagnosis was based on one serum specimen showing an elevated MAT titer ($\geq 1:200$). None of the patients were diagnosed by culture or immunofluorescence.

The presumptive infecting *Leptospira* serogroup was defined by MAT in all patients. The predominant serogroup was Icterohaemorrhagiae, which infected 8 (40%) of 20 patients.

FIGURE 2. Percentage of travel-related cases of the total number of annual leptospirosis cases diagnosed in Israel during 2002–2008 (n = 48). * Annual percentage in Israel during 1985–1999.⁹

TABLE 1
Demographic and epidemiologic characteristics of sporadic leptospirosis cases among travelers*

Characteristic	Leshem and others (this study)	Van Crevel and others ⁷	Total
Number	20	32	52
Nationality	Israeli	Dutch	
Location where acquired			
Southeast Asia	15 (75%)	28 (87%)	43 (82%)
Latin America and the Caribbean	0	3 (9%)	3 (6%)
Africa	2 (10%)	1 (3%)	3 (6%)
Oceania	2 (10%)	0	2 (4%)
Central America	1 (5%)	0	1 (2%)
No. males	18 (90%)	26 (81%)	44 (84%)
Mean age, years	28	31	29.9
Water-related activity	16/18 (89%)	31 (96%)	47/50 (94%)
Hospitalized	20 (100%)	25 (78%)	45 (86%)
Antibiotic treatment	17/18 (94%)	14 (44%)	31/50 (62%)
Mortality	0/20	0/32	0/52
Serogroup			
Icterohaemorrhagiae	8	4	12
Sejroe	3	5	8
Australis/Autumnalis	1	6	7
Bataviae	1	2	3
Pyrogenes	3	1	4
Canicola	2	0	2
Hardjo	1	0	1
Tarassovi	1	0	1

*The features of 20 travelers reported in the current series are compared with a previous series with similar epidemiology (n = 32).

Seven of these eight cases were acquired in Thailand and Laos. The other serogroups are shown in Table 1.

The type and prevalence of symptoms of leptospirosis among our patients is summarized in Table 2. Notably, fever and headache were the most prevalent, gastrointestinal symptoms were common, and conjunctivitis was present in a few patients. Mean $\pm$ SD duration of fever was 5.8 ± 1.7 days (range = 4–10 days).

Severe disease manifested as renal failure, respiratory failure, or meningitis was present in 10 (55%) of 18 patients. Acute renal failure was present in 8 (44%) of 18 patients, one of whom required hemodialysis. Respiratory failure was diagnosed in 2 (11%) of 18 patients, one of whom required mechanical ventilation. Meningitis was present in one patient (5%).

The severe manifestations were significantly more common among travelers presumptively infected with Icterohaemorrhagiae serogroup compared with those infected with *Leptospira* of the non-Icterohaemorrhagiae serogroup (7 of 8 versus 3 of 10, respectively, odds ratio = 16.3, 95%

TABLE 2
Symptom prevalence among 18 patients with travel-related leptospirosis, Israel

Symptom	No. (%)
Fever	18 (100)
Headache	15 (83)
Fatigue	13 (72)
Nausea and vomiting	12 (66)
Myalgia	12 (66)
Arthralgia	7 (39)
Diarrhea	7 (39)
Chills	5 (28)
Rash	5 (28)
Conjunctivitis	4 (22)
Cough	3 (17)

confidence interval = 1.3–197, $P = 0.02$). Patients infected with *Icterohaemorrhagiae* serogroup had also significantly longer hospitalizations compared with patients with non-*Icterohaemorrhagiae* serogroup (mean $\pm$ SD = 8 ± 3 days versus 4.9 ± 3.3 days, respectively; $P = 0.05$).

Detailed laboratory results are shown in Table 3. Platelet counts were significantly lower in patients infected with presumptively *Icterohaemorrhagiae* serogroup.

Treatment consisted of doxycycline in 11 (61%) of 18 patients, penicillin in 3 (17%) of 18, and amoxicillin/clavulonate, ceftriaxone and azithromycin, and ciprofloxacin in one patient each; one patient received no treatment. All patients were hospitalized. None of the patients died and all had a complete recovery.

DISCUSSION

The epidemiology of leptospirosis has been changing in recent years. Although the incidence of leptospirosis is steadily decreasing in developed countries, there is a re-emergence of the disease in tropical and subtropical regions.^{1,9,15–20} Factors attributed to the decrease in the incidence of leptospirosis in developed countries include improvement in sanitation, mechanization of agricultural methods, and prevention of occupational exposures at risk. At the same time, travel-related leptospirosis has been emerging as a major cause of infection in developed countries.^{7,16,21} In our study, 42% of leptospirosis cases diagnosed in Israel during 2002–2008 were acquired during travel abroad. This finding is a significant increase in the percentage of cases related to travel compared with 1 (1.7%) of 59 cases during 1985–1999 reported in a nationwide study of leptospirosis in Israel (Figure 2).⁹ During the study years, the proportion of travel-related cases continued to increase, reaching 83% of the cases during the last year of the study (Figure 2). Reports of leptospirosis mainly in the 1990s from Germany, the Netherlands, and Hawaii documented travel-related leptospirosis in 16%, 14%, and 6% of the cases, respectively.^{7,16,21} These rates seem similar to the rate reported in Israel during those years. However, to the best of our knowledge, no reports exist regarding the percentage of travel-related cases in recent years.

The average yearly incidence of leptospirosis acquired in Israel during the study years (0.06/100,000 inhabitants) was similar to the attack rate was previously reported in Israel during 1985–1999.⁹ However, the estimated incidence of travel-related leptospirosis was 1.78/100,000 travelers per year, which reflected a risk ratio of 29 for travel-related leptospirosis. Thus, travel appears to be an important risk factor for

acquiring leptospirosis. This finding was also reported by Jansen and others in a summary of leptospirosis in Germany, where travel abroad was the single most important exposure risk identified.¹⁶

The rate of travel-related leptospirosis showed significant increase during the study years (Figure 2). This increase may represent an increasing number of travelers to highly endemic areas or an increase in risky exposures during adventure travel. Such exposures may be water-related activities during recreational tourist or sports events.^{2,3} Another possible cause of the increase in the diagnosis of travel-related leptospirosis is an increase in awareness among travel medicine practitioners of leptospirosis as a cause of fever in returned travelers.

The serologic diagnosis of leptospirosis requires a high level of suspicion and often repeated serologic tests. Because the MAT is a complex test to maintain, perform, and interpret, it is only performed in specialized reference laboratories. In the setting of acute febrile illness, a final diagnosis is not always achieved. Moreover, no data exist regarding leptospirosis seroconversion in returned travelers, and there is no estimation the true burden of illness exists in this population. In a recent study summarizing the causes of fever in 6,957 ill returned travelers, only 25 (0.3%) cases were diagnosed with leptospirosis.²² A similar rate was shown in another large series of febrile returned travelers in which 6 (0.3%) of 1,842 patients were diagnosed with leptospirosis.²³ In a series of hospitalized returned Israeli travelers, 2 (1.2%) of 163 patients had leptospirosis.²⁴ The rate of unspecified febrile illness was 16–24% in the three series. It is possible that underdiagnosis of leptospirosis contributed to this large proportion of unspecified febrile travelers in these series.

Most cases of travel-related leptospirosis in the literature are described in outbreak settings.^{2,3,25,26} Only one previous report summarized the characteristics of sporadic travel-associated leptospirosis.⁷ Two series of sporadic travel-related leptospirosis are summarized in Table 1. Several important features are common to both series: the predominance of cases acquired in Southeast Asia, male predominance, the fact that most cases were acquired during water-related exposures, the high hospitalization rate, and the predominance of cases presumptively caused by serogroup *Icterohaemorrhagiae*.

Many travelers to tropical countries participate in water-related activities such as rafting, kayaking, tubing, and swimming. Thailand and Laos have large numbers of visitors, and water-related activities are popular among travelers to these countries. This finding may explain that most cases in both series were acquired in those areas. Male predominance was noted in our series and in the Dutch series, which might be

TABLE 3
Laboratory results of 18 travelers with leptospirosis, Israel*

Result	Mean $\pm$ SD, all patients (n = 18)	Non- <i>Icterohaemorrhagiae</i> serovar (n = 10)	<i>Icterohaemorrhagiae</i> serovar (n = 8)	P
Leukocyte count, $\times 10^3/\text{mm}^3$	9.2 $\pm$ 3.9	9.4 $\pm$ 4.2	8.9 $\pm$ 3.7	0.8
Hemoglobin, g/dL	12.9 $\pm$ 1.7	13.4 $\pm$ 1.8	11.7 $\pm$ 0.8	0.1
Platelet count, $10^3/\text{mm}^3$ (reference value $> 140 \times 10^3/\text{mm}^3$)	166 $\pm$ 74	196 $\pm$ 62	115 $\pm$ 68	0.02
Creatinine, mg/dL (reference value < 1.5 mg/dL)	2.5 $\pm$ 2	1.9 $\pm$ 1.6	3.3 $\pm$ 2.3	0.1
Total bilirubin, mg/dL (reference value < 1 mg/dL)	1.9 $\pm$ 1.6	1.7 $\pm$ 1.8	2.1 $\pm$ 1.4	0.6
AST, IU/L (reference value < 47 IU/L)	74 $\pm$ 52	82 $\pm$ 52	62 $\pm$ 53	0.4
ALT, IU/L (reference value < 53 IU/L)	89 $\pm$ 56	99 $\pm$ 59	75 $\pm$ 51	0.3

*AST = aspartate aminotransferase; ALT = alanine aminotransferase.

explained by a possible over-representation of males in adventurous (water-related) activities during travel. Interestingly, a recent report indicated that male sex was associated with a higher severity of clinical leptospirosis.²⁷ This finding could not be evaluated in our cohort because of a small number of females.

Water-related activities were identified in most of the Israeli patients. However, 2 (11%) of 18 patients did not participate in such activities. Thus, any febrile traveler must be asked specifically about water exposure. Moreover, leptospirosis should be suspected in any traveler with undifferentiated febrile illness even when water exposure is not reported.

Presumptively, the most common infecting serogroup in our patients was Icterohaemorrhagiae. When we summarized cases in both series of travel-related leptospirosis, infection with serogroup Icterohaemorrhagiae accounted for 12 (23%) of 52 of the cases. We suggest two possible reasons for the dominance of infection with this serogroup. The first is that patients infected with serogroup Icterohaemorrhagiae may seek medical assistance and require hospitalization more frequently because of severity of the infection. The other possible reason is the high incidence of infection with serogroup Icterohaemorrhagiae in Thailand and Laos. In a recent survey conducted in northern Thailand, patient serum samples reacted predominantly with the *bratislava*, *autumnalis*, and *icterohaemorrhagiae* serovars.²⁸ However, in several studies reporting serologic surveys in local populations in Southeast Asia, serogroup Icterohaemorrhagiae was not shown to be the dominant serogroup.^{29–32}

Leptospirosis was seen as multi-organ failure and a potentially life-threatening disease in many of our patients. This type of manifestation was significantly more common in patients presumptively infected with serogroup Icterohaemorrhagiae. Van Crevel and others also reported that jaundice and renal failure were more common in patients infected with serogroup Icterohaemorrhagiae than with non-Icterohaemorrhagiae serogroups in travelers.⁷

There were no fatal cases despite severe disease and organ failure in many of our patients. In previous reports of travel-related leptospirosis, no deaths were reported.^{2–7,25,26} It is possible that the risk of death is low in such cases because of the healthy nature of the average traveler population, especially those engaging in water sports and adventure travel, or the better medical care in industrialized countries.

The major limitation of our study is a possible selection bias. Only patients with severe illness were hospitalized and underwent full evaluation including repeated serologic analysis. Thus, the proportion of severe cases may be overestimated in our series. Many travelers with mild, self-limiting illness may have remained undiagnosed. In addition, the diagnosis of leptospirosis usually requires a convalescent-phase serum sample that is frequently not available. Taken together, the disease burden in travelers is probably underestimated.

In conclusion, travel-related leptospirosis has emerged as the predominant cause of leptospirosis in Israel in recent years. Travelers and clinicians must be educated about the risks of fresh water exposure especially during travel to tropical areas. Leptospirosis may manifest as undifferentiated febrile disease in the returned traveler, but some cases have severe forms with renal failure and respiratory failure. Because of the nonspecific nature of the initial manifestation, a high level of suspicion is required to make the diagno-

sis. Antibiotic treatment should be initiated before definitive diagnosis because treatment shortens the duration of illness and reduces mortality.^{33,34}

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APPENDIX 1

Leptospira serovars tested (Serogroup, serotype, and origin)

Serovars of *L. interrogans*

Icterohaemorrhagiae, Wijnberg M 20, Tropical Institute Amsterdam; Icterohaemorrhagiae, RGA, ATCC-43642; Canicola, Hond Utrecht IV, ATCC-23470; Grippothyphosa, Moscow V, ATCC-23469; Hebdomadis, Swzajizak, Tropical Institute Amsterdam; Hebdomadis, Sejroe M 84, Central Public Health London; Hardjo, Hordjoprajitno, Denmark; Pomona, ATCC-23478; Bataviae, ATCC-23468; Rachmat, ATCC-23478; Javanica, Veldrat, ATCC-233479; Australis, ATCC-23605; Cynopteri, Canalzone, Walter Reed USA; Pyrogenes, ATCC-23480; Ballum, Castelloni, ATCC-23580; Ballum, Mus, Atlanta; Tarassovi, ATCC-23481; Balcanica, Burgas 1627, Neville; Sejroe, Bratislava, Mr. Hirsh (Kmety); Autumnalis, Rachmat, Tropical Institute Amsterdam

Serovars of *L. biflexa*

Patoc I, Semarang, Holland; Andamana, CH 11