Studying Risk Factors Associated with Human *Leptospirosis*

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ABSTRACT

Background: *Leptospirosis* is one of the most under diagnosed and underreported disease in both developed and developing countries including India. It is established that environmental conditions and occupational habit of the individuals put them at risk of acquiring disease, which varies from community to community. Various seroprevalence studies across the world have documented emerging situation of this neglected tropical disease, but limited have probed to identify the risk factors, especially in India. **Objectives:** The objective of this study was to identify the environmental and occupational risk factors associated with the disease in Udupi District. **Materials and Methods:** This population-based case-control study was carried out in Udupi, a District in Southern India from April 2012 until August 2012. Udupi is considered to be endemic for *Leptospirosis* and reported 116 confirmed cases in the year 2011. Seventy of 116 laboratory confirmed cases and 140 sex matched neighborhood healthy controls participated in the study. A predesigned, semi-structured and validated questionnaire was used for data collection through house to house visit and observations were noted about environmental conditions. Univariate analysis followed by multivariate analysis (back ward conditional logistic regression) was performed by using STATA version 9.2 (StataCorp, College Station, TX, USA) to identify potential risk factors. **Results:** Occupational factors such as outdoor activities (matched odds ratio [OR] of 3.95, 95% confidence interval [CI]: 1.19-13.0), presence of cut or wound at body parts during work (matched OR: 4.88, CI: 1.83-13.02) and environmental factors such as contact with rodents through using the food materials ate by rat (matched OR: 4.29, CI: 1.45-12.73) and contact with soil or water contaminated with urine of rat (matched OR: 4.58, CI: 1.43-14.67) were the risk factors identified to be associated with disease. **Conclusion:** *Leptospirosis* is still considered as neglected disease in the district. Early diagnosis and prompt treatment of cases can save many lives. However, there is a need of integrated rodent control measures with great effort to increase awareness and education among subjects in controlling the disease.

Key words: Case-control study, India, *Leptospirosis*, Population

INTRODUCTION

Leptospirosis is a neglected zoonotic infectious disease caused by spirochetes of genus *Leptospira,* which can be transmitted directly or indirectly though human-to-human transmission is not common.[1] Being sporadic in nature, it has been reported as the outbreak from developing countries such as Nicaragua, India, Brazil, Thailand, Sri Lanka[2-5] and from urban areas of developed countries such as USA,[6] France,[7] Japan,[8] Ireland[9] and Germany.[10] Studies have identified that peak incidence of disease occured during rainy seasons in tropical regions and late summer to early fall in temperate regions, but most of the time outbreak followed periods of excess rainfall.[1] Besides mentioned climatic factors certain occupation or professions s such as farming,[11] butchering,[12] veterinarians[13] and rodent control[14] put individuals at risk for disease. It is estimated that presently one billion of the world's population live in the slum area, which is going to be doubled by 2025 can have a significant impact on the *Leptospirosis* disease burden.[15]

In South East Asia, 447 million people are engaged with agriculture in rural areas of 11 different countries.[16] Most of the countries[17,18] sharing similar environmental, cultural and demographic characteristics have reported well number of cases in past few years, which is again anecdotal just like a tip of the iceberg. India lacks data on national incidence of *Leptospirosis*, even though the disease contributes for 12.7% of acute febrile illness.[19] Since, 1980 different states

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from India have been reporting cases of *Leptospirosis* as mini endemic situations.[19] Southern India with favorable climatic conditions for inhabitation of spirochetes is considered as endemic region past 29 years.[20,21]

Karnataka, a South Indian state had reported 224 cases in total with 19 deaths during the year 2005 [Unpublished data, District Surveillance Unit, Udupi] majority of which was contributed by Udupi District. With on an average every year nearly, 100 cases are being registered in different laboratories of the district Udupi has reported 367 number of cases from 2009 to 2011 (District Surveillance unit, Udupi). Although the basic determinants of the disease are common, the magnitude and nature of these factors vary from environment-to-environment, which pre-disposes of having specific factors for the disease for specific community. At present, there are few seroprevalence studies carried out in India, but very few efforts was made to identify underpinning risk factors, which necessitates for an analytical study in order to have better insight in identifying and understanding the factors responsible for transmission of the disease and developing effective strategies for prevention and control in the community. Keeping local cultural and environmental context in view, present matched case-control study was an attempt to identify the environmental and occupational risk factors associated with disease.

MATERIALS AND METHODS

Study area

Udupi constitutes total population of 1,177,908 and density of 304 persons/km^2.[22] The district is geographically surrounded by Arabian Sea in west and nearly, 65% of the land is covered with forests and hilly area (Western Ghat hills). The district receives earliest rainfall after Kerala in India with on an average 444 mm in a year within 10 months and average temperature of 35°C.[23] Being a notifiable disease in the district all suspected cases of fever with jaundice were screened for the disease through immunoglobulin M enzyme linked immune sorbent assay for one or more samples by using Panbio Lepto kit (Pan-Bio, Queensland, Australia.) having sensitivity and specificity of 85% and 90% respectively. District surveillance unit had documented complete information of all positive cases reported form corners of the district along with Kasturba Medical College (KMC), a tertiary care hospital.

Case definition

A case was defined as any laboratories confirmed positive cases reported in the district during the period 1st January 2011-31st December 2011.

Exclusion criteria

Individuals who migrated in or out at least 1 month before the disease appeared and any suspected case and persons having a history of any other viral disease such as Dengue, JE were excluded from the study.

Control definition

Individuals, who were disease negative, residing in same locality and did not migrate during the appearance of disease in cases, were considered as control. Any suspected cases, previously diagnosed patient and patients having symptoms of *Leptospirosis* were excluded from the study.

Study design

Prior to initiation of the study line listing of the cases were done. Permission letter was obtained from the district health officer and institutional ethical committee. Appointment was taken from concerned medical officers of the primary health centers. Health workers in the area were intimidated through medical officer to locate the house of the case. Brief description was given to the health workers before visiting the houses. Questionnaires and informed consent was translated to Kannada (Local language) in order to avoid language bias. Maximum three attempts were made to visit the houses of cases including one on holidays, failure of which the case was excluded from the study.

Selection of cases and controls

Among 116 positive confirmed cases reported in the district, subjects who met the criteria of case definition were included in the study. High non-response rate was anticipated due to lack of information on migration and other factors at reporting unit, because of which all individual houses were visited. For each case, two sex matched controls were selected for the study from the neighborhood. Group matching of sex was done (±10 years) due to the increased chances of not getting the control.

First control was selected from the house situated next right to house of the case within 50 m of radius and fulfilling the inclusion criteria and agreed to participate in the study. Second control was also selected in same manner, but beyond 50 m radius of the first control's house. Effort was taken to ensure that the control was not migrated in from any other area during last 1 month of diagnosis of the case. Gender, age and geographical area of living were thought to be confounders, which were adjusted by matching during recruitment of study subjects. Cases and

controls were interviewed after getting informed consent. Inclusion of cases and controls are described in Figure 1.

Data collection and study tools

A predesigned semi structured questionnaire was used for data collection having consistent reliability (Chronbach alpha 0.8) piloted prior to the study. Questions were asked about socio-demographic information, nature of job, contact with the vehicle during the work, protection measures taken during the work, presence of animals at home, the type of contact with the animals, presence of rodents at home/work place, types of contact and environmental factors such as the presence of drainage within 15 m radius of house, presence of garbage within 15 m radius of the house, taking a bath in stream or pond or river and type of house.

Occupation of last 1 month before getting the disease was asked in detail in term of type and duration, which was classified later on into indoor and outdoor type based upon their nature of the job. The presence of animals and rodents during the period of acquiring the disease was enquired and quantified according to respond.

Statistical analysis

Univariate odds ratio (OR) for the potential risk factors were calculated by using matched univariate conditional logistic regression method with 95% confidence interval (95% CI) in STATA 9.2 software (StataCorp, College Station, TX, USA). Factors having significant $P < 0.05$ were included for further analysis. Backward elimination method was used variables had highest insignificant values were excluded step wise form the analysis. Conditional multiple logistic regression was carried out to identify independent risk factors by using STATA 9.2 software. Variables in the model with significance $P < 0.05$ were identified as a potential factor for the disease.

RESULTS

A total of 70 confirmed cases and 140 healthy neighborhood controls participated in the study.

Age of the participants ranged from 13 to 76 years. Out of 70 cases, 27 (38.6%) were female and 43 (61.4%) were male. The mean age of study participant was 44.61 years [Table 1].

Out of 20 cases, 6 (28.6%) belonged to age group 41-50 and 14 (20%) were within the age group 21-30 years. 91.4% of the cases and 92.9% of controls were Hindu by religion. Out of 70 cases only (8.6%) 6 cases were tribal by ethnicity. Nearly, 33% of the cases and 30% of controls used to stay in mixed type of house, which was defined as, a house with a roof made up of asbestos or tiles, but the walls are not cemented. Kutcha house was defined as a house having a thatched roof and non-cemented floor. 25.7% of the cases mentioned to have Kutcha houses. 59 out of 70 cases used well-water for drinking purpose, whereas 11 cases used tube well or tap water for drinking purpose. 96.6% of cases had open well-compared to 89.7% controls [Table 2].

Table 1: Characteristics of the study participants

Variables	Category	Cases (total = 70)	Control (total = 140)
		Number (%) or mean (SD)	Number (%) or mean (SD)
Age	Female	43.37 (±14.15)	43.41 (±13.75)
	Male	45.40 (±13.81)	46.23 (±14.28)
Sex	Female	27 (38.6)	54 (38.6)
	Male	43 (61.4)	86 (61.4)

SD: Standard deviation

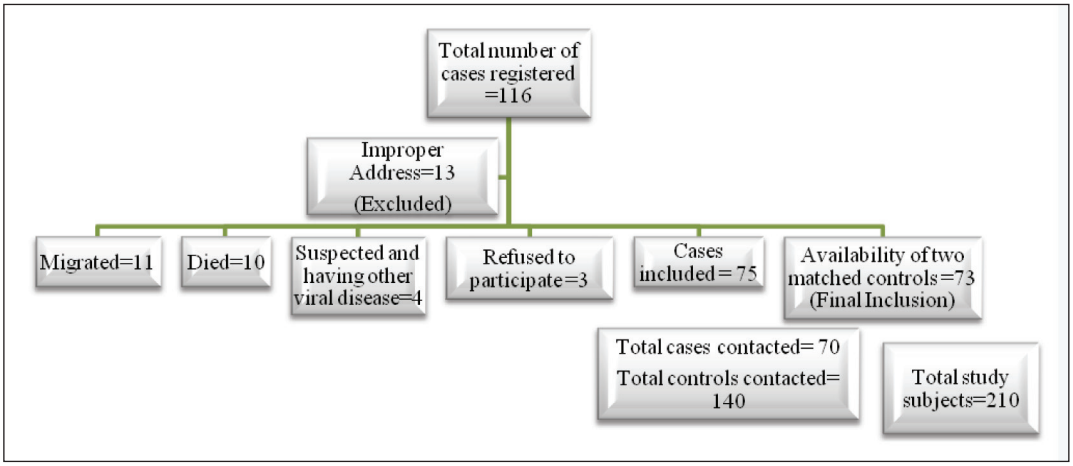

Figure 1: Inclusion of cases

Table 2: Prevalence and univariate analysis of risk factors

Category	Case (70) Number (%)	Control (140) Number (%)	Crude OR (95% CI)	*P* value
Ethnicity (schedule tribe)	6 (8.6)	9 (6.4)	5.5 (0.41-74.5)	0.193
Staying in Kutcha houses	18 (25.7)	37 (26.4)	1.65 (0.65-4.16)	0.285
Staying in mixed type house	33 (47.1)	42 (30)	2.63 (1.26-5.49)	0.010**
Use of well-water for drinking purpose	59 (84.3)	116 (82.9)	1.16 (0.45-2.95)	0.752
Use of open well-water	57 (96.6)	105 (89.7)	2.8 (0.57-14.3)	0.196
Outdoor type of job	16 (20)	64 (45.8)	3.04 (1.53-6.03)	0.001***
Crosses water on the way to job	54 (77.1)	93 (66.4)	1.86 (0.9-3.8)	0.093
Direct contact with water or mud during work	51 (72.9)	72 (51.4)	3.33 (1.62-7.6)	0.001***
Spending >8 h/day at work in water	17 (33.3)	6 (8.2)	2.1 (0.8-5.5)	0.131
Use of protective measures during work	1 (1.4)	7 (5)	0.28 (0.03-2.32)	0.241
Presence of cut or wound during work	53 (75.5)	37 (26.4)	8.6 (4.03-18.47)	0.001***
Taking bath in river/stream after work	28 (40)	24 (17.1)	4.56 (2.01-10.31)	0.001***
Presence of domestic animals at home	42 (60)	61 (45.6)	1.21 (1.02-1.43)	0.023*
Residence of animal shed within 15 m radius of house	17 (40.5)	17 (27.9)	2.35 (0.85-6.49)	0.098
Handling the animal excreta in bare hand	10 (23.8)	5 (8.2)	2.86 (0.58-13.96)	0.192
Presence of dog at home	41 (58.5)	83 (59.2)	1 (0.53-1.56)	1
Presence of >3 cats at home	1 (4.8)	27 (56.2)	0.11 (0.01-1)	0.05*
Presence of rodents inside home	42 (60)	11 (8)	22.6 (4.7-108)	0.001***
Presence of rodents at work place	4 (4.7)	19 (13.9)	0.38 (0.12-1.8)	0.096
Use of vegetables ate by rodents	26 (37.1)	27 (19.7)	4.6 (2.11-10.02)	0.001***
Contact with soil contaminated with urine	26 (37.1)	22 (16.07)	5.9 (2.6-13.5)	0.001***
Seeing >5 rats per day	38 (54.3)	7 (5.1)	103.9 (19.6-549.6)	0.001***
Presence of drainage within 15 m radius of home	36 (52.9)	95 (67.8)	3.69 (1.62-8.41)	0.002**
Presence of garbage within 15 m radius of home	26 (37.1)	36 (18.6)	2.42 (1.05-5.57)	0.001***

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. OR: Odds ratio, CI: Confidence interval

Univariate analysis was performed to determine the strength of association for potential risk factors [Table 2].

Environmental factors

Individuals stayed in mixed type of house were having unadjusted OR of 2.63 (95% CI: 1.26-5.49) compared to Pukka house dwellers. Analysis was carried out for the source of drinking water might be responsible for the disease categorized as well and other source (tube well, tap water, tanks and bore well). It was found that the unadjusted OR for using well-water for drinking purpose was 1.16 (95% CI: 0.45-2.95). Usage of open well-water was not found to be significant for *Leptospirosis* though there was chance of contamination of water. The presence of drainage and garbage within 15 m radius of houses had OR of 3.69 and 2.42 respectively [Table 2].

Occupational factors

For analysis purpose occupation was categorized as indoor and outdoor activities. Outdoor activities were found to be a significant risk factor compared with indoor job with OR of 3.04. Crossing water on the way to job had an unadjusted OR of 1.86 (95% CI: 0.9-3.8) did not put individual at risk; however, direct contact with water or mud during work, presence of cut or wound in body parts in contact with water or mud and taking a bath in the river or stream after work were found to be significant. Use of protective measures could not be considered for analysis as there was only one case, mentioned of using boot during work [Table 2].

Exposure to animals and rodents

Exposure to animals could be a potential risk factor for the disease. In the present study, rearing domestic animals at home was identified as a risk factor with an unadjusted OR of 1.21 (95% CI: 1.02-1.43). The presence of rodents and seeing more than five rats per day at home or work place were found to be risk. Practices such as use of vegetables ate by rats, contact with contaminated soil with rat's urine surrounding home were found to be highly associated as an independent factor [Table 2].

Multivariate analysis

Multivariate conditional logistic regression was carried out to identify potential risk factors after adjusting for confounding. Out of 12, 10 variables which had $P < 0.05$ in univariate analysis were considered for multivariate analysis. Two variables (presence of rat inside the home and seeing >5 rats per day) were excluded because of wider CI. Backward elimination method was adopted for multivariate analysis. Variables with highest *P* value were eliminated stepwise until all variables had significant $P < 0.05$.

The presence of cut or wound in body parts during work and having contact with soil contaminated with urine of rodents were found to be highly significant with an adjusted OR of 6.05 (95% CI: 2.09-15.3) and 4.86 (95% CI: 1.65-14.3) respectively. Occupational factor like outdoor activities and environmental factor like the presence of drainage within 15 m radius of the home were identified as potential risk factors. Practices like usage of food materials ate by rodents also seen to be associated with *Leptospirosis* with an adjusted OR of 3.53 (95% CI: 1.34-9.28) [Tables 3 and 4].

DISCUSSION

In our study, majority of the case belonged to age group 41-50 and 21-30 years, which falls into productive age group. Acquiring infection during this period can have economic impact on the family as well in country as reported in a study from Brazil.[24] Risk factors such as the presence of cut or wound, outdoor occupation, contact with rodents through usage of contaminated food materials, contact with contaminated soil and presence of drainage within 15 m of radius from home were found to be responsible for the disease [Table 4]. Even though, controls were selected from the neighborhood environmental factors such as contaminated soil, and presence of drainage emerged to be crucial.

Among all, the strongest risk factor identified was the presence of the wound or cut in the skin during the work. It was observed that almost none of the cases used any kind of protective measure (wearing boot or gloves) during work. Possible reasons for the same could be due to most of the agriculture activities in India are still done by the human beings and long way to be mechanized. There is tradition of carrying out cultivation in bare foot and hand with the help of animals such as cows, which creates risk of getting injury and direct contact with contaminated mud. Similar findings were documented in Thailnad,[25] having wound in skin had an OR of 3.97 for getting the disease. We observed that most of our cases had cracked foot and uprooted foot nails creating an opportunity for direct entry of *spirochetes*. Occupations such as agriculture, masons and carpenters have high chances of getting injury to body part while working, which again increases the chances of entry of the microorganism. Bharadwaj *et al*.[26] in their study also showed contact of injured part with water had OR of 6.69 (95% CI: 3.05-14.64) getting the *Leptospirosis*. Studies form Pune[27] and France[7] also reported skin abrasion as a common factor for getting infection. Encouragement for the use of protective measures such as gloves, gum boots can reduce the chances of getting the disease, which again needs more sensitization and education targeting the risk groups. However, from cultural and social aspect of India, this needs much more push from policy level to individual level for an effective result to be seen. Other measures such as prophylaxis of doxycycline or techniques such as protecting body parts using other chemicals needs to be explored and studied scientifically.

Contact with contaminated soil around home was the second highest risk factor for the disease. In Indian scenario, it is commonly observed that people occasionally use any foot wear while they work in surrounding to their home. The presence of high number of rodents surrounding the home increases chances of contamination of the soil with infected urine. While walking bare foot with skin abrasion further enhances the opportunity of getting infection. Similar finding was reported in Andaman and Nicobar Island study.[28] Eating of vegetables by rats indirectly indicates dense rodent population and directly pre-disposes to contamination. Lack of safe use practice before eating the food exposes the individual into more risk of getting the disease.

Table 3: Multivariate conditional logistic regression with back elimination method

Category	Case (70) Number (%)	Control (140) Number (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	*P* value
Staying in mixed type house	33 (47.1)	42 (30)	2.63 (1.26-5.49)*		
Direct contact with water or mud during work	51 (72.9)	72 (51.4)	3.33 (1.62-7.6)**		
Outdoor type of job	16 (20)	64 (45.8)	3.04 (1.53-6.03)**	3.86 (1.38-10.7)	0.010**
Presence of cut or wound during work	53 (75.5)	37 (26.4)	8.6 (4.03-18.47)	6.05 (2.29-15.30)	0.001***
Taking bath in river/stream after work	28 (40)	24 (17.1)	4.56 (2.01-10.31)**		
Presence of domestic animals at home	42 (60)	61 (45.6)	1.21 (1.02-1.43)*		
Presence of >3 cats at home	1 (4.8)	27 (56.2)	0.11 (0.01-1)*		
Use of vegetables ate by rodents	26 (37.1)	27 (19.7)	4.6 (2.11-10.02)**	3.95 (1.4-11.24)	0.010**
Contact with soil contaminated with urine	26 (37.1)	22 (16.07)	5.9 (2.6-13.5)**	4.86 (1.65-14.3)	0.004**
P Presence of drainage within 15 m a radius of home	36 (52.9)	95 (67.8)	3.69 (1.62-8.41)*	3.86 (1.4-16.09)	0.013*
Presence of garbage within 15 m radius of home	26 (37.1)	36 (18.6)	2.42 (1.05-5.57)**		

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. OR: Odds ratio, CI: Confidence interval

Table 4: Identified occupational and environmental risk factors associated with *Leptospirosis* in Udupi district

Factors	Adjusted OR	95% CI	*P* value
Presence of cut or wound during work	6.6	2.75-15.86	0.001
Outdoor type of job	3.86	1.38-10.7	0.010
Use of vegetables ate by rodents	3.5	1.3-9.28	0.011
Contact with soil contaminated with urine	4.45	1.62-12.2	0.004
Presence of drainage within 15 m radius of home	3.88	1.2-12.19	0.020

OR: Odds ratio, CI: Confidence interval

Occupational factor such as outdoor jobs involve direct contact with soil, mud or water during work putting individuals at risk. Studies such from Thailand[25] and Andaman Island[21] have documented it positively. It is expected that only outdoor job could not be the cause of the disease. The presence of the wound or cut in body parts, contact with infected materials act synergistically making more vulnerable for disease. A study carried out by Vijayachari *et al*.[29] in Andaman Island also reported similar kind of result.

Environmental sanitation and hygiene is a proven factor being responsible for the disease. Similarly in our study, we observed that the presence of drainage within 15 m radius of the home was a risk factor. Udupi receives heavy rainfall during the rainy season for 10 months in a year. During the rainy season, there occurs overflow of the sewage or drainage making the environment more contaminated. A study conducted in Salvador Brazil[30] shared similar result having proximity to open sewer increases the risk by 5 times. This proximity favors inhabitation of rodents and microorganism creates a threat to the environment coupled with other personal factors stimulate the disease cycle. Hygiene practices at individual level, such as boiling of water before drinking, avoidance of open ground defecation, avoidance of bathing at highly risk areas such as streams and rivers and protective measures against rodent contact to food can play a vital role in preventing the disease.

The study was limited by the case identification protocol based on the list of cases with *Leptospirosis* registered in the district during 2011 year. Owing to the lack of resources controls were not tested, but utmost care was taken during selection of controls to reduce the bias. Ability to recall among cases and controls could not be same and might have recall bias. The cultural practice and environment is same in many part of the state so it could be generalized.

Future implication for policy and program

Risk factor for the disease in every community is inextricably woven to its environmental fabric. Current policies for *Leptospirosis* focus on early detection of cases and prompt management. No doubt this restricts mortality and complications at early stage, but this can be strengthened if coupled with integrated rodent control approach. Identification of risk zones such as tourist places, fields, rivers, streams and imparting proper awareness emphasizing risk groups people could be beneficial. Amidst a plethora of interventions to prevent neglected tropical diseases, which is getting more neglected, integrated rodent control are yet to be mainstreamed in the developing countries. There is also need of research to understand the potential reservoir because of diversity of the reasons. Development of electronic database, integration of private, government hospitals and academic research organizations and application of geographic information systems can be helpful in understanding the distribution of the disease in the state. Frontline health workers could be explored as a channel for disseminating education at the community, fostering their work with basic skills and knowledge for risk factor recognizing, timely reporting.

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