

# LEPTOSPIROSIS DISEASE BURDEN ESTIMATION AND SURVEILLANCE NETWORKING IN INDIA

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**Abstract.** Although leptospirosis is known to have occurred in India since the early years of the 20<sup>th</sup> century, no accurate data on disease burden exist. During the past two decades, leptospirosis cases have been reported with increasing frequency from different parts of the country. Several large outbreaks have occurred. In the year 2000, the Indian Council of Medical Research set up a Task Force on Leptospirosis. The Task Force conducted a multi-centric study on disease burden due to leptospirosis. As part of the study, 3,682 patients with acute febrile illness, from 13 different centers in India, were investigated for the presence of current leptospiral infection using the Lepto-dipstick test. Of these patients, 469 (12.7%) were found to have leptospiral infection. The positivity rate ranged from 3.27% in the central zone to 28.16% in the southern zone. Fever, body aches and chills were the common symptoms observed. Urinary abnormalities, such as oliguria, yellow discoloration of urine and hematuria were found in 20%-40% of patients. Distribution of serogroups was studied based on microscopic agglutination test (MAT) titers. The southern zone had all the eleven serogroups in the panel, the eastern zone had nine, the northern zone eight, and the central and western zones had five circulating serogroups each. Among various risk factors studied, rat infestation of houses had the strongest association with leptospiral infection. Many other factors related to the environment, personal and occupational habits, etc. also had significant associations. The study had a few drawbacks. The Task Force has decided to continue the study with modified protocols to generate more accurate and detailed information about disease burden.

## INTRODUCTION

### Early reports

The existence of leptospirosis in India was suspected during the early years of the 20<sup>th</sup> century (Chowdry, 1903; Woolley, 1913; Barker, 1926). Confirmatory proof came from the Andaman Islands, when Taylor and Goyle (1931) isolated leptospire from the blood and urine of 24 patients among the free-living convicts of what was then a penal settlement. Reports followed from major metropolises such as Calcutta and Bombay (Dasgupta and Chopra, 1937; Dalal, 1960) and a few other areas (Franklin, 1918; Mahanthy, 1945). During the 1950s, 60s and 70s there were only a few reports of the disease from India. The reports during this period were mostly of the disease in animals.

### Upsurge in the 1980s

During the early 1980s, reports of leptospirosis cases started appearing with increasing frequency from some areas of India, particularly from the southern state

of Tamil Nadu. Leptospirosis was found to be a common cause of febrile illness and jaundice in Madras city during the monsoon season (Ratnam *et al*, 1983b). High seroprevalence rates were observed in high risk groups such as conservancy workers. Epizootics and small outbreaks in humans also were reported in some areas in Tamil Nadu (Ratnam *et al*, 1983a).

In late 1980s, a febrile illness with hemorrhagic manifestations started appearing as outbreaks during the post-monsoon season every year in the Andaman Islands. For five years, the cause of the disease remained unknown and it was called Andaman hemorrhagic fever (AHF) (Directorate of Health Services, 1993). A study carried out during an outbreak in 1993 showed that the affected persons had serological evidence of current leptospiral infection, thus establishing the leptospiral etiology of the disease (Sehgal *et al*, 1995). This was the first report of leptospirosis with pulmonary involvement from India. Serological studies conducted among healthy individuals in areas affected by the outbreaks showed that a large proportion of the population was seropositive to leptospiral antibodies (Sehgal *et al*, 1994; 2000).

During the 1990s, leptospirosis cases were being regularly reported from most of the southern states (Venkataraman *et al*, 1992; Kuriakose *et al*, 1997; Prabhaker *et al*, 1997; Rathinam *et al*, 1997) and from

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some areas elsewhere (Madhusudhana and Bhargawa, 1988; Sahni *et al*, 1995; Barua *et al*, 1999; Singh *et al*, 1999). The outbreaks of AHF were continuing in the Andaman Islands. Leptospirosis was found to be the common cause of clinical syndromes, such as acute renal failure (Muthusetupathy *et al*, 1991; 1994) myocarditis (Ramachandran and Perera, 1977) and uveitis (Sivakumar *et al*, 1996; Rathinam *et al*, 1997).

### Outbreaks

The earliest recorded outbreak of leptospirosis in India occurred among bund construction workers in a village in South Andaman, in 1929 (Taylor and Goyle, 1931). Outbreaks of leptospirosis in the form of Andaman hemorrhagic fever are still common occurrences in South and North Andaman. In 1997 and 1998, there were major outbreaks in Surat District, Gujarat. It occurred in the same areas where an outbreak had occurred the previous year, which was widely publicized as an outbreak of pneumonic plague. In 1999, the state of Orissa, on the east coast of India, was affected by a major cyclone. Following this, many villages were flooded due to heavy rainfall. An outbreak of febrile illness with high fatality rate was reported in the flooded villages about a fortnight after the cyclone. An investigation conducted four weeks later among the residents of the flooded villages showed that about 20% of them had serological evidence of recent leptospiral infection (WHO, 2000; Sehgal *et al*, 2002). In the year 2000, the west coastal districts of Maharashtra received unusually heavy rainfall and the cities of Mumbai and Thane were flooded. An outbreak occurred after the floods and serological and bacteriological studies showed that it was due to leptospires. In 2000 and 2001, the incidence of leptospirosis recorded a sharp increase in many districts in the state of Kerala. A few small confined outbreaks were also reported from Tamil Nadu.

### Indicators of disease burden

Leptospirosis is not a notifiable disease in India and, therefore, no accurate disease incidence figures are available. In some areas, where it has been recognized as an important public health problem, reporting systems have been established in recent years. These include Tamil Nadu, Kerala and the Andaman and Nicobar Islands. One major problem in these reporting systems in Tamil Nadu and Kerala is that the reporting is done only by hospitals and clinics run by the Government. The private sector, which serves a major portion of the population, has no participation in the system, and hence its sensitivity is low.

In the Andaman and Nicobar islands, the private

sector does not have a strong presence as a health service provider and hence the reporting system has better sensitivity. The data from this reporting system show that leptospirosis is the third most common cause of hospital deaths. The incidence of clinically diagnosed leptospirosis, as per the reporting system, ranges between 40-80 cases per 100,000 persons per year. Seroprevalence ranges between 30% to 60% and the results of limited follow-up studies show that the incidence of infection is very high in the islands (Murhekar *et al*, 1998).

The study conducted after the cyclone in Orissa indicated that about 20% of the residents of the flooded villages had symptomatic leptospiral infection during the post-cyclone period. In Kerala, during the past two years, more than 6,000 cases have been reported by different Government hospitals (personal communication).

Other than these estimates in limited populations and indirect indicators, no data on disease incidence exist in India. However, these indicators show that leptospirosis is a common cause of febrile illness in many parts of the country, particularly in coastal and low-lying areas. The unavailability of diagnostic facilities, and the lack of awareness about the disease, were the major reasons for overlooking the possibility of leptospiral infection as a cause of febrile illness. Consequently, the incidence of the disease has been grossly underestimated.

### Task Force on Leptospirosis

The Indian Council of Medical Research (ICMR) constituted a Task Force on Leptospirosis with the objective of assessing indicators of disease burden. The Regional Medical Research Center at Port Blair, Andaman and Nicobar, which had been designated as the National Leptospirosis Reference Center, was assigned the task of coordinating the Task Force project on disease burden estimation. The Task Force carried out a study on the role of leptospirosis as a cause of febrile illness in different parts of the country.

## MATERIALS AND METHODS

### Task Force study on disease burden due to leptospirosis

The estimation of disease burden was envisaged to be conducted in a phased manner. The overall objectives of the Task Force Project were to estimate the morbidity and mortality indices specific to leptospirosis, and to assess the determinants of disease occurrence, including the factors pertaining to the bacteria, reservoirs, host and environment.

**Phase I.** Phase I was confined to assessing the proportion of leptospirosis cases among all cases of febrile illness attending the selected hospitals/centers. This indicator was chosen because of the operational problems in conducting population-based studies. In the absence of any information about incidence and mortality rates, the proportional case ratio gives some indication of the magnitude of the problem. Phase I was conducted during the period January-December 2001.

**Participating centers.** Initially, 15 centers were identified to participate in the study. Later, two of them withdrew and the study was initiated with 13 centers. These centers represented almost all regions of the country. The distribution of the participating centers and the states covered by the centers is shown in Fig 1. The cities/towns served by the participating centers together had a population of over 68 million, while the states covered had a population of 637 million. Details of the population covered by the participating centers in each region are shown in Table 1.

**Sampling.** Each participating center was to induct 600 patients into the study during a period of one year. The number of patients inducted should be equally distributed in each month. Thus, each center was required to induct 50 patients fulfilling the criteria each month. With thirteen centers participating, this adds up to 7,800 patients. This would allow estimation of the proportional case ratio separately for each center with the anticipated accuracy.

#### Criteria for clinical diagnosis

Any patient reporting with fever of acute onset with

generalized body aches and headache associated with any of the following symptoms/signs was suspected as a case of leptospirosis:

1. Cough and hemoptysis
2. Unexplained breathlessness
3. Any bleeding tendencies including sub-conjunctival hemorrhage
4. Jaundice or laboratory evidence of liver dysfunction
5. Oliguria or laboratory evidence of renal dysfunction
6. Signs of meningeal irritation



Fig 1- Participating centers and the states represented in Phase I of the ICMR Task Force study on disease burden due to leptospirosis in India.

Table 1

Details of populations in cities/towns covered by the participating centers in each region, patients included in the study and dipstick positivity rate (done at the coordinating center).

Region	Population covered		Patients	Positive (%)
	Cities	States		
Northern	5,350,953	177,023,690	348	27 (7.76)
Western	4,611,586	106,349,246	810	32 (3.95)
Central	1,230,640	49,876,124	306	10 (3.27)
Eastern	14,011,902	143,566,498	929	37 (3.98)
Southern	9,741,512	160,300,118	1,289	363 (28.16)
Total	34,946,593	637,115,676	3,682	469 (12.74)

### Laboratory investigations

Lepto-dipstick tests (Gussenhoven *et al*, 1997; Sehgal *et al*, 1999) were done on acute samples and on a follow-up sample taken 7-10 days after the first clinical examination. The Lepto-dipstick test was chosen because of its simplicity and the relatively low skill required. Besides, the results would be relatively observer-independent, as the test employs internal controls.

The microscopic agglutination test (MAT) (Wolff, 1954) was to be done on paired samples taken 7-10 days apart. The included patients were asked to report to the hospital a second time to obtain the follow-up sample. MAT was done using a panel of antigens representing eleven serogroups prevalent in India. The serogroups represented were Australis, Autumnalis, Ballum, Bativiae, Canicola, Grippotyphosa, Hebdomedis, Icterohaemorrhagiae, Javanica, Pamona, and Sejroe. MAT on all the serum samples was done at the National Reference Center to avoid inter-laboratory variations in reading standards.

### Determinants of leptospiral infection

Information about several socio-cultural, occupational and environmental factors was collected from patients included in the study.

## PRELIMINARY RESULTS

### Inclusion of patients and diagnosis

Patient inclusion at the 13 participating centers was terminated a year after the initiation of the project. Although 7,800 patients had to be included in the study as per the protocol, only 3,682 patients were actually included during the study period. The participating centers identified 569 (15.04%) patients having current leptospiral infection, based on the results of Lepto-dipstick tests done on acute or convalescent samples. The Lepto-dipstick test was repeated at the National Reference Center for all patients reported positive by the centers. The results were positive for 469 (12.7%) patients (Table 1). When the results were compared patient to patient, the dipsticks done at the participating centers had 99.4% sensitivity (95% CI: 98.0-99.8%), 96.8% specificity (95% CI: 96.1-97.4%), 81.9% predictive value positive (95% CI: 78.4-84.9%) and 99.9% predictive value negative (95% CI: 99.7-100.0%). The overall agreement between the diagnoses at the participating centers and coordinating center was 97.1% with a  $\kappa$  value of 0.8813 ( $Z=53.82$ ,  $p < 0.01$ ).

### Microscopic agglutination test

Although the original plan was to solely depend

upon MAT results on paired samples for diagnosis, in practice it was not possible as a second sample could not be obtained from about one-third of the patients, who gave positive results by dipstick. About 75% of the patients who gave positive results by dipstick were also positive by MAT. The serogroups against which the samples gave titers differed from place to place. Serogroups Australis and Grippotyphosa were present in 10 of the thirteen states. Autumnalis, Ballum and Canicola were present in nine states. All the serogroups except Bativiae were present in the State of Kerala, whereas Jodhpur in Rajasthan, and Srinagar in Kashmir, had only two and three serogroups, respectively. The distribution of the serogroups in different states is summarized in Table 2.

### Common clinical features

The common symptoms and signs observed among confirmed patients are summarized in Table 3. The most common symptom/sign among patients was fever (100%) followed by body ache (83.8%) and chills (71.22%). Urinary abnormalities such as oliguria (38.81%) and yellow discoloration of the urine (37.1%) were the next common symptoms. Bleeding tendencies other than hematuria were rare, with less than 2% of the confirmed patients reporting any of them.

### Determinants of disease occurrence

The prevalence of various risk factors and their association with the presence of leptospiral infection was estimated in a sub-sample of the cases from whom complete data on these factors were available. These patients were mainly from the states of Kerala, Karnataka, Maharashtra and Andhra Pradesh. The univariate odds ratios of these factors are shown in Table 4. Rat infestation had the highest odds ratio (5.82) followed by farming family (own agricultural land), house close to river and mud-walled houses. Only preliminary analysis was done on the risk factor data. Further analysis, including checking for collinearity between factors and calculating independent risk estimates using multiple logistic modeling etc, are in progress.

## DISCUSSION

The Phase I study was intended to generate baseline data on disease occurrence in various parts of India. In spite of the operational problems in carrying out a study involving many centers in the country, the study generated useful information about the existence of leptospirosis in different parts of the country. The project also generated some information about the common clinical presentation and factors associated

Table 2  
Distribution of different leptospire serogroups in each region.

Center	Infesting serogroups (by MAT) <sup>a</sup>										
	Aus	Aut	Bal	Bat	Can	Gri	Ict	Sej	Pom	Jav	Heb
Central											
Eastern											
Northern											
Southern											
Western											

<sup>a</sup> Aus: Australis; Aut: Autumnalis; Bal: Ballum; Bat: Bataviae; Can: Canicola; Gri: Grippotyphosa; Ict: Icterohaemorrhagiae; Sej: Sejroe; Pom: Pomona; Jav: Javanica; Heb: Hebdomedis.

Table 3  
Common symptoms/signs among patients who were positive by leptospire dipstick done at the coordinating center.

Symptom	Proportion
Fever	100.0
Body ache	83.8
Chills	71.2
Oliguria	38.8
Yellow urine	37.1
Diarrhea	27.5
Headache	25.6
Conjunctival suffusion	25.4
Icterus	25.0
Cough	23.0
Dyspnea	20.5
Hematuria	19.6
Vomiting	19.4
Pallor	17.1
Muscle tenderness	8.7
Sub-conjunctival hemorrhage	4.3
Arrhythmia	4.3
Dyspnea	2.6
Hemoptysis	2.1
Petechial hemorrhage	2.1
Neck stiffness	1.7

with leptospiral infection. Presumptive information about the leptospiral serogroups circulating in different parts of the country was also generated.

Because of the lack of representativeness of the study sample, the information cannot be generalized

to the population of the country. The study was purely hospital-based. In most cases, it was based on tertiary level hospitals. Because of the difference in the accessibility of different social classes of population to these hospitals, there would be a selection bias in favor of people living in urban and semi-urban areas. Assessing determinants of leptospiral infection was only a subsidiary objective and the study design did not allow a proper case-control analysis. The laboratory techniques employed in the Phase I study were based on serology. Although these techniques are relatively easier and have good accuracy in diagnosing leptospiral infection, they lack the ability to detect the characteristics of the infecting organism. The characterization of leptospire circulating in different parts of the country and the assessment of the geographical distribution of different genotypical and phenotypical variants of the organism can be useful in planning control strategies.

Usually the serological screening tests have acceptable sensitivity. However, if the sample is taken very early in the course of the disease and a second sample is not available, the sensitivity of serological tests like the dipstick can be low. The Phase I study showed that obtaining paired samples from all patients is very difficult in practice. If the availability of paired samples is a strict requirement, about half of the patients included in the Phase I study would have to be removed from analysis. In subsequent phases of the study, other tests that have the ability to detect infection very early should be incorporated. The best option would be to use a combination of tests to increase the range of timing when the sensitivity remains high. New tools, like PCR, have good sensitivity during the early phase of disease and can

Table 4  
Risk factors significantly associated with leptospiral infection.

Factor	OR	95% CI		p-value
		Low	High	
Rat infestation of house	5.82	3.55	9.63	0.00000
Owens agricultural land	5.46	3.73	8.03	0.00000
River nearby house	4.77	3.61	6.3	0.00000
Mud-walled house	4.35	2.71	7.07	0.00000
Recent field work	3.77	2.87	4.95	0.00000
Bathes in pond	3.59	2.72	4.73	0.00000
Water bodies on the way to house	3.10	2.38	4.05	0.00000
Use of stream water for washing	2.97	2.13	4.15	0.00000
Farmer	2.49	1.87	3.31	0.00000
Poultry farming	2.29	1.77	2.97	0.00000
Use of well water for washing	2.12	1.64	2.75	0.00000
Manual laborer	1.70	1.2	2.4	0.00167
Ponds in house compound	1.69	1.28	2.24	0.00010
Habitual drinker	1.62	1.19	2.21	0.00139
Mud flooring of house	1.44	1.1	1.89	0.00502
Handle domestic animals	1.43	1.11	1.84	0.00440

be incorporated into the diagnostic process.

#### Future plans

The Task Force on Leptospirosis has decided to continue the study on disease burden. In the next phase, necessary modifications will be made to the protocol to address the problems identified during the first phase. New methods, like PCR, will be incorporated into the screening method. Part of the study will be population-based. The other objectives set during the formation of the Task Force, such as studying the distribution of various genotypic and phenotypic variants of leptospire in different parts of the country, looking for environmental vehicles of infection etc, will be incorporated into the next phase. The tentative objectives of the next phase are the estimation of the prevalence of symptomatic and asymptomatic leptospirosis in different parts of the country, estimation of the proportion of cases with leptospiral etiology among cases of specific clinical syndromes such as acute renal failure, atypical pneumonia and uveitis, assessment of risk factors of infection and complications and characterization of circulating strains in different parts of the country.

The study will be conducted in both high-endemic and low-endemic areas. The monitoring setup will be more decentralized, by improving the capabilities of the regional centers. The next phase will also have

components of molecular epidemiology. The Task Force project has helped to develop a network of centers for monitoring the occurrence of leptospirosis in India. It has also developed a pool of technical manpower with skills in performing various diagnostic tests for leptospirosis. This infrastructure and these capabilities will finally be incorporated into a national surveillance network for leptospirosis.

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