Review Article

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Leptospirosis among the self-supporting convicts of Andaman Island during the 1920s - the first report on pulmonary haemorrhage in leptospirosis?

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Several researchers had carried out investigations on the possibility of existence of Weil's disease in Andaman Islands during early 20th century. The first report of a series of confirmed cases of leptospirosis that occurred during1929 was published in 1931.There were several reports during 1995 to 2009 that described detailed account of leptospirosis including various clinical syndromes. The possibility of pulmonary involvement in leptospirosis being a manifestation historically overlooked rather than newly emerged during the past two decades is examined in this review in the context of Andaman Islands. Two case series of leptospirosis, one occurred in 1929 and the other in 1996-1997 were reviewed with special emphasis on pulmonary involvement and haemorrhagic manifestations. The similarities and differences in the clinical profile of patients of the two case series were analysed. The review shows that respiratory system involvement and pulmonary haemorrhage as evidenced by presence of haemoptysis as a complication of leptospirosis was occurring during 1920s in Andaman Islands. The incidence of pulmonary involvement, however, rose from 9.4 per cent during 1929 to 52 per cent in 1996-1997. The case fatality ratio in patients with pulmonary involvement, which was 50 per cent during 1929 and 42.9 per cent during 1996-1997, was higher than that in cases without pulmonary involvement.Fever, conjunctival congestion, jaundice, vomiting, diarrhoea, hepatomagaly, haemoptysis, haematemesis and subconjunctival haemorrhage were common in both series. The case series in Andaman Islands in 1929 was probably the first report of pulmonary haemorrhage as a manifestation of leptospirosis. The increase in the incidence of pulmonary involvement in leptospirosis in the recent past is probably due to the increase in the density and diversityof its animal vectors,the broadening of the range of circulating serovars and the interactions between the vector and the agent. An increased virulence of *Leptospira* through gene acquisition and loss on an evolutionary time scale and the resulting change in the gene content, gene order and gene expression cannot be ruled out.

Key words Leptospirosis - pulmonary haemorrhage - self-supporting convicts - Weil's disease

Andaman and Nicobar Islands

The archipelago of Andaman and Nicobar Islands (92-94ºE; 6-14ºN), a chain of more than 500 islands, is situated in the Bay of Bengal about 1200 km south-east of the Indian peninsula. Before colonization by British, the islands were inhabited by several native tribal groups belonging to both mongoloid and negrito racial stocks[1].

Colonization and population growth

Colonization of the islands started in 1858 when a batch of 700 convicts was brought by the British rulers to clear the land and construct a prison. Once the prison was built, batches of convicts were regularly brought to the islands to serve their term in the infamous cellular jail. Well-behaved prisoners could, after serving in various levels of confinement and forced labour, eventually became self-supporting convicts with their own agricultural land and they were sometimes allowed to raise families[2]. With the arrival of thousands of convicts and deployment of officials to administer these islands, the local population swelled to more than 18,000 by the turn of the 20th century. There was a lull in the population growth between 1901 and 1921 due to cessation of transportation of convicts in 1906[1]. After 1921 the Andaman experienced a steady growth of population until 1941.

During the post-independence era, the population of the islands grew at a rapid pace as immigrants from various parts of India and neighbouring countries settled in different islands. In 1949, refugees from East Pakistan were brought under the rehabilitation scheme by the Government of India. Till 1962, under this rehabilitation programme, 2644 families were settled in colonies located in different islands[1]. The total population of Andamans increased to 48,985 in 1961, 93,468 in 1971, 1,58,287 in 1981, 2,41,453 in 1991, and 3,56,265 in 2001[3,4].

Early reports of leptospirosis

The earliest report of cases with fever and jaundice in Andaman dates back to 1892[5], six years after Adolf Weil published his account of the clinical syndrome characterized by jaundice, nephritis and splenomegaly[6], which was later proved to be due to *Leptospira*. Chowdry in 1903[7] reported a series of 588 cases of jaundice complicating malaria occurring in Andaman during a period of 10 years from 1892. Barker (1926)[8] and Taylor and Goyle (1931)[5] reviewed description of these cases and concluded that these were essentially cases of Weil's disease. The features of the cases that favoured the possibility of Weil's disease were occurrence of jaundice after the subsidence of fever in many cases, high fatality rates, presence of conjunctival congestion typical of Weil's disease, marked prostration, tendency for haemorrhages, albuminuria and autopsy findings typically seen in Weil's disease[5]. The cases sometimes occurred in epidemics[5]. The overall case fatality ratio in Chowdry's case series was 13.2 pre cent[7]. Woolley[9,10] reported a series 40 similar cases with 17 deaths (CFR: 42.5%) occurred in 1909 among self-supporting convicts living near swamps, which he described as cases of malaria though they were negative for malarial parasite in peripheral blood and in liver and spleen of fatal cases. The clinical descriptions of these cases were similar to that of Weil's disease. In 1921, de Castro[11] observed five similar cases, who had heamatemesis and bleeding from gums as well, looked for *Leptospira* in blood films but was not successful in demonstrating them. Barker (1926)[8] was the first to report microscopic evidence of *Leptospira* in stained specimens of urine and in films from liver of fatal cases. However, his guinea pig inoculation experiments did not succeed. Deuskar[12] reported 23 cases of Weil's disease treated at Haddo Hospital in 1926. Brown[13] reported that serum sample obtained on 19th day of illness from a fatal case in Andaman gave positive adhesion test with two Sumatra strains of *Leptospira viz,*. Rachmat A and Deli A. Autopsy specimens from the same case showed organisms similar to *Leptospira* in renal tubules.

Cases between 1923 and 1929

Taylor and Goyle (1931)[5] reported data on 266 cases of Weil's disease occurred in Andaman between 1923 and 1929 (no data were available for 1925). Number of cases by month of occurrence is shown in Fig. 1. Most of the cases occurred during the period August – November when the Southwest monsoon was active, though in some years, cases occurred during December-January months as well, when the Northeast monsoon sets in. Fig. 2 shows this seasonal pattern in the occurrence of Weil's disease and the average monthly rainfall during the previous 25 years. The occurrence shows a larger peak in October and a smaller one in December.

The population of the settlement during this period was about 16,000 including about 8,000 convicts, 7,200 free resident population and 1,700 administrative personnel. The annual number of cases reported ranged between 11 to 92 giving an overall annual incidence of 69 to 575 per 100,000 population[5]. However, the

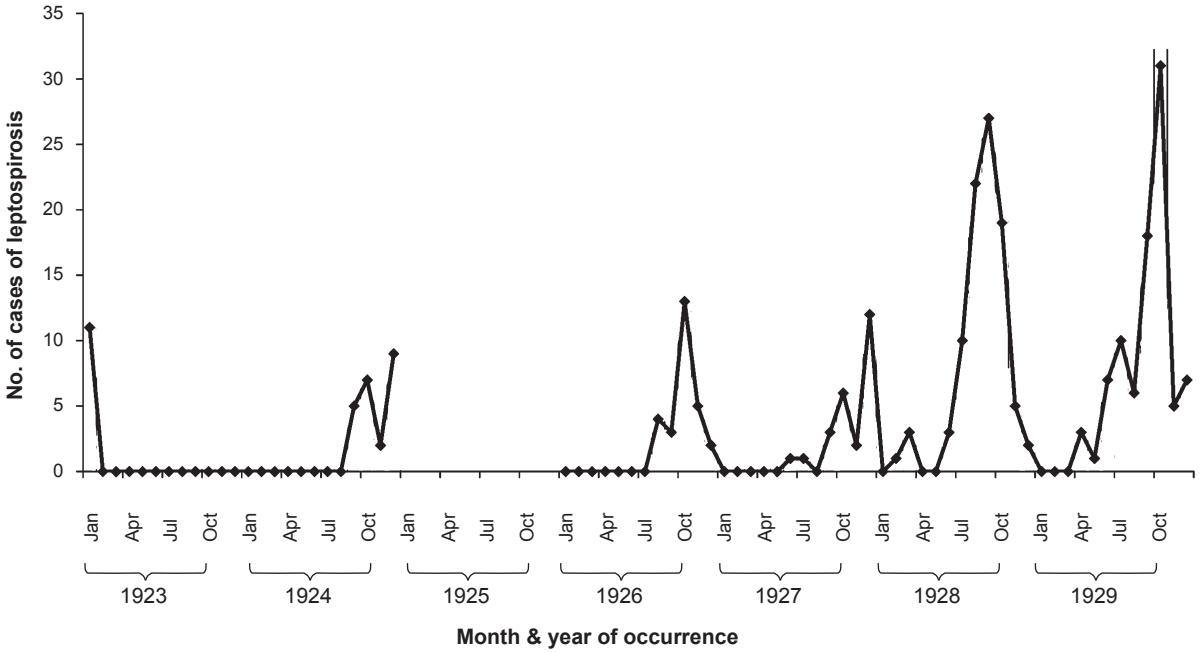

Fig. 1. Distribution of cases of Weil's diseases reported in Andaman between 1923 and 1929 by month of occurrence
Source of data: Ref 5.

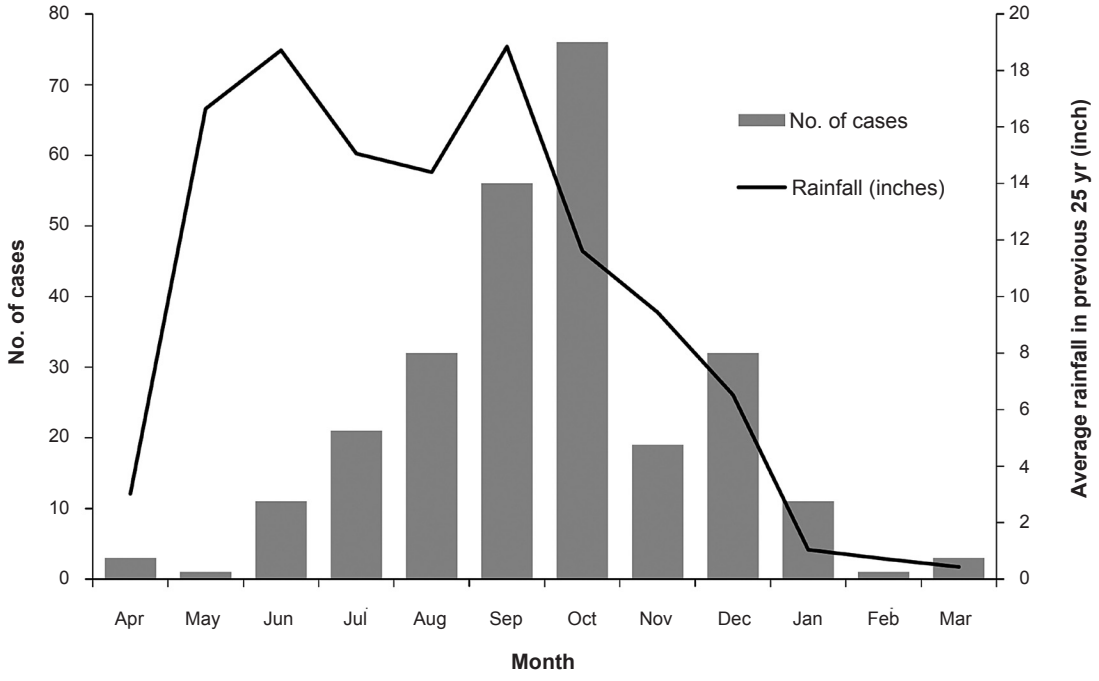

Fig. 2. Seasonal trend in the occurrence of Weil's disease (data for 1923-1929 pooled by month of occurrence, no data available for 1925) and average monthly rainfall during the previous 25 years. *Source of data*: Ref. 5.

cases mostly occurred among self supporting convicts. Therefore, the incidence of Weil's disease among the self supporting convicts, whose population was only 8,000 would have been several fold higher. While the self supporters lived in 75 small villages scattered throughout the settlement, the 'free settlers' lived in separate villages.

Investigations in 1929

Taylor and Goyle (1931)[5] carried out investigations based at Ross General Hospital during a five months period starting from June 1929. The salient observations of the authors along with the results of some further analysis of the data contained in the publication are presented here.

The total population of Andaman settlement at that time was 16,878 including 7,901 convicts, 7.200 free settlers and 1,777 administrative staff. Among the convict population, 5,531 were labouring convicts who were engaged in various works necessary for the construction and maintainance of the amenities of the settlement. Another 2,043 of the convicts were self-supporting convicts, primarily engaged in agriculture[5].

During the period of investigations, all suspected cases of Weil's disease occurring in the settlement were transferred to Ross General Hospital as early as possible and detailed investigations were carried out for each case[5]. This included detailed clinical examination and complete blood and urine examination, blood culture for isolation of *Leptospira* and guinea pig inoculation. Special serological tests and examination of centrifuged urine were carried out later. In fatal cases, autopsy was performed and heart blood was cultured. Emulsions of liver and kidney were examined under darkground microscopy as well as by light microscopy after staining by Levaditi technique[5].

A total of 73 suspected cases were seen by the investigators, but a diagnosis of Weil's disease was made only in 64 cases[5]. Among these 64 confirmed patients of leptospirosis, 61 were self-supporting convicts. Among these 64 patients, 12 died giving a case fatality ratio of 18.75%; 24 (37.5%) were categorized as mild cases, 28 (43.75%) as moderately severe and the remaining 12 (18.75%) as severe. While all severe cases were fatal, all the moderately severe and mild cases recovered. Occurrence of cases by month and severity is shown in Fig. 3.

Fever: The median duration of fever for all the cases was seven days and the mean was 7.9 days (95% CI: 7.04, 8.77). The median duration of fever for mild and severe cases was six days while that for moderately severe cases was nine days. The lower median duration of fever for severe cases as compared to moderately severe cases was because of the deaths of the severe cases early. Temperature was irregular and in the range of 101°F to 104°F in the first few days of illness and by second week usually the temperature touched baseline except in those cases where a relapse or a recrudescence of fever occurred, which was observed in 12 (18.75%) cases. The temperature during the relapse was not as high as the initial rise[5].

Jaundice: Jaundice was observed in 42 (65.6%) cases[6], it was mild in eight, moderate in 20 and severe in 14. Jaundice commonly appeared on 4th-5th day, but occasionally appeared as late as on the 9th day.

Other organ involvement: Bradycardia was observed during early convalescent period. Five cases had irregular heart rate including two who had extra systoles. Two fatal cases had atrial fibrillation two days before death. These five cases probably had myocarditis and in fatal cases that had atrial fibrillation, the cause of death could probably be myocarditis and cardiac failure[5].

The investigators stated that as a rule there was no evidence of respiratory complication, though in six cases haemoptysis had occurred and three of these cases were fatal. Thus the incidence of pulmonary involvement in this case series was 9.4 per cent (95% CI: 3.5, 19.3) and the case fatality ratio among them was 50 per cent. A typical severe and fatal case described by the authors had developed haemoptysis on the 5th day of illness and had ronchi all over the lungs. He had another bout of haemoptysis on the 6th day and on the 7th day he had massive haematemesis and died. Post-mortem examination showed sub-endocardial, sub-pleural and sub-peritoneal haemorrhages as well as haemorrhages into small and large intestines.

Gastrointestinal (GI) system involvement included haematemesis and melena, which were recorded in two and five cases each, nausea and vomiting were recorded in nine patients and diarrhoea in five cases. Marked abdominal tenderness, particularly in upper abdomen was observed in many cases and probably was due to some degree of gastritis. The stomach of one fatal case was full of mucous and blood on post-mortem examination and another fatal case had severe haemorrhagic diarrhoea.

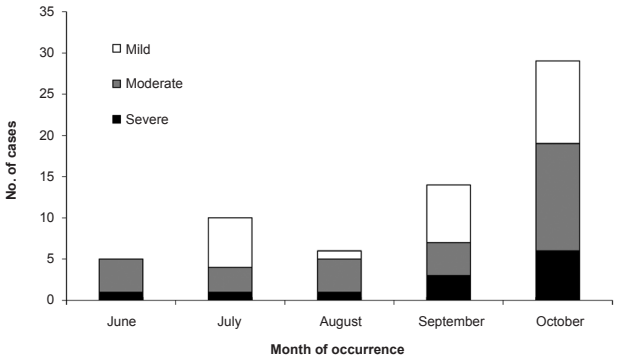

Fig. 3. Occurrence of cases of Weil's disease during 1929 by month and severity. *Source of data*: Ref 5.

Oliguria occurred in most cases, though complete anuria was observed only in a few cases. Albuminuria was present in 50 per cent of cases. The authors suggested that there was some association between jaundice and albuminuria with icteric cases usually having albuminuria and anicteric cases free from it. Hyaline and granular casts were seen frequently on microscopy of centrifuged deposit of urine and in one case RBC casts were seen.

Occurrence of neck stiffness or altered sensorium was not recorded, but common occurrence of extreme prostration as a possible result of nervous system involvement was mentioned. Muscle pains all over the body and severe calf muscle tenderness were recorded in a large proportion of cases (61 of 64). No superficial lymph node enlargement, more than that seen usually among the population, was noticed. However, in post-mortem examination, mesenteric nodes were seen to be enlarged, congested and occasionally haemorrhagic. Sub-conjunctival infection was noted in most cases.

Clinical manifestations and case fatality ratio: The case fatality ratios by organ involvement among patients were calculated with 95 per cent confidence intervals and the results are summarized in Table I. Since the numbers in some of the categories are small, the rates need to be interpreted with caution. Of the 64 cases in the series, 42 had various grades of jaundice and 22 did not have. All the 12 deaths occurred among the cases that had jaundice, thus giving a case fatality ratio of 28.6 per cent (95% CI: 15.7, 44.6) for cases with jaundice. Haemorrhages occurred in 13 (20.3%) cases and among them six died giving a case fatality ratio of 46.2 per cent (95% CI: 19.2, 74.9). Respiratory system involvement as evidenced by presence of haemoptysis and gastrointestinal system involvement evidenced by presence of haematemesis or melena occurred only in patients who had jaundice also. Six patients had haemoptysis and among them three died giving a case fatality ratio of 50 per cent while gastrointestinal system involvement was present in seven cases, of whom six died giving a case fatality ratio of 85.7 per cent. Involvement of both respiratory system and gastro-intestinal system was present in three patients and all of them died (CFR: 100%). Although the numbers were small to demonstrate statistical significance of difference in case fatality ratios, these indicated that involvement of respiratory system, gastrointestinal system or occurrence of any form of haemorrhages were predictors of mortality. The risk of death apparently was the highest when both respiratory and gastrointestinal system involvements were present and when the involvement of these systems occurred in isolation, gastrointestinal system involvement posed a higher risk of death as compared to respiratory system involvement.

Continuous exposure and haemorrhages: A subgroup of 18 patients included in the series by Taylor and Goyle (1931)[5] was part of a common-source outbreak occurred in a village called Mithakari and these patients were involved in construction of a bund. They were apparently continuously exposed to stagnant water during their work hours as they were standing in water while constructing the bund. Among these 18 patients, six (33.3%) developed some form of bleeding manifestation. The incidence of bleeding manifestation among the remaining 46 patients was much lower (7/46, 15.2%). The case fatality ratio among the patients who were bund construction workers was 22.2 per cent while that among the other patients was 15.0 per cent. Two of the three fatal cases with haemoptysis also occurred among this group of 18 patients, while the other case occurred among the remaining 46 patients. Similarly, four of the seven patients with gastrointestinal GI bleeding occurred among the 18 patients engaged in bund-construction work giving an incidence of 22.2 per cent for GI bleeding among them while the incidence of GI bleeding among the rest of the patients was only 6.5 per cent . These were probably early indications that prolonged contact with stagnant water leading to continuous exposure to *Leptospira* and/or large inoculum sizes might increase the risk of haemorrhages and pulmonary involvement in leptospirosis. Occurrence of haemorrhagic manifestations and death among patients belonging to

Table I. Cases, deaths and case fatality ratio (CFR) among patients with various bleeding manifestations calculated from the data presented by Taylor & Goyle (1931)[5] and Singh *et al* (1999)[14]

	1929[6]				1996-1997[14]			
Syndrome	Cases	Deaths	CFR	95%CI	Cases	Deaths	CFR	95%CI
Only fever	22	0	0.0					
Fever with Jaundice	42	12	28.6	15.7, 44.6	30	2	6.67	0.8, 22.1
Fever with haemoptysis					28	12	42.86	24.5, 62.8
Fever with jaundice and haemoptysis	6	3	50.0	11.8, 88.2				
Fever with jaundice and gastrointestinal (GI) bleed (haematemesis or malena)	7	6	85.7	42.1, 99.6				
Fever with jaundice, haemoptysis and GI bleed	3	3	100.0	29.2, 100.0				

different occupation groups were calculated and the results are summarized in Table II.

First indication of pulmonary involvement in leptospirosis: Although the investigations were primarily on Weil's disease in Andaman[5], the case series described contained a large number of anicteric cases, which would not have passed for a clinical diagnosis of Weil's disease. The criteria for including these cases in the case series are not very clear from the report[5]. Haemorrhages appear to be an important determinant of death in Weil's disease as the case fatality ratio among cases with haemorrhages (46.2%) was four-times higher than that among cases without haemorrhages (11.8%). Haemoptysis, indicating involvement of respiratory system, was present in approximately 10 per cent of the cases and the case fatality ratio in these cases was 50 per cent. Cases with gastrointestinal bleeding had a much higher case fatality ratio of 85.7 per cent. Gastrointestinal bleeding in cases of Weil's disease has also been observed earlier by de Castro[11]. Pulmonary involvement as evidenced by occurrence of haemoptysis appeared to be an important determinant of death in the case series of Taylor and Goyle (1931)[5]. This probably was the first indication of the predilection of leptospirosis to affect the respiratory system and cause fatal pulmonary haemorrhage, which after several decades, was recognized as a separate clinical syndrome of leptospirosis, first in China and Korea[15] and then in other parts of the world[16,17].

Re-emergence in 1980s

Very little information was available about the status of leptospirosis in Andaman after the report by Taylor and Goyle (1931)[5]. In the post-monsoon season of 1988, an outbreak of a disease characterized by fever, haemorrhages and respiratory symptoms occurred in a forest labour camp at South Andaman, which soon spread to rural areas adjoining Port Blair. A similar outbreak occurred in another focus in North Andaman about 300 km away from Port Blair (unpublished data, DHS). The aetiology of the disease was unknown at that time and remained so for the next five years though the outbreaks recurred every subsequent post-monsoon season with predictable punctuality. Serological investigations conducted during the outbreak occurred in 1993 showed that the aetiology was *Leptospira*[16]. Further proof for the leptospiral aetiology was later

Table II. Haemorrhages and mortality among patients from different occupational categories calculated from the data presented in Taylor & Goyle (1931)[5]

Occupation	Cases	Deaths	CFR	Haemorrhages	(%)
Bund construction	18	4	22.2	6	33.3
Agriculture	26	3	11.5	4	15.4
Other occupations	20	5	25.0	3	15.0
Total	64	12	18.8	13	20.3

CFR, case fatality ratio

obtained through isolation of the organism from the blood of patients who had similar disease[18].

Leptospirosis is now a recognized public health problem in Andaman islands[19]. Cases occur as clusters and outbreaks during the post-monsoon season as well as during the inter-epidemic periods. When it appeared as outbreaks with predominant pulmonary involvement in 1988, two focuses were involved *viz.* the rural areas adjoining Port Blair in South Andaman and Diglipur town and adjoining areas in North Andaman. A few new focuses have emerged such as Rangat[20] town and Billiground village in Middle Andaman. Severe cases from accessible areas are usually referred to the only referral hospital in the Union Territory, G.B. Pant Hospital at Port Blair.

Severe cases of leptospirosis reported in 1996-1997

Singh *et al*[14] carried out a detailed clinical study of a series of severe cases of leptospirosis admitted to G.B. Pant Hospital, Port Blair. The study prospectively recruited all suspected cases of leptospirosis attending the hospital during a 12 month period and investigated the cases for leptospirosis. A detailed clinical work up was done for all confirmed cases. A total of 80 patients fulfilling a clinical case definition of leptospirosis were enrolled and screened for leptospirosis and 58 patients fulfilled the laboratory diagnostic criteria based on isolation of *Leptospira* from blood or four-fold rise in titre/seroconversion in microscopic agglutination test (MAT). Among these patients, 46 (79.3%) were from rural areas near Port Blair and 27 (46.5%) were exposed to rice field and another 13 (22.4%) to other wet and water-logged environments[14].

Among the 58 patients included in the study, 14 died resulting in a case fatality ratio of 24.1 per cent. Thirteen of the 14 deaths occurred among the patients from rural areas and the case fatality ratio among the patient from rural areas was 28.2 per cent, while the CFR of patients from urban areas was 8.3 per cent. Two distinct clinical syndromes were noticeable among the patients, a pulmonary syndrome and a hepato-renal syndrome, though some degree of overlap occurred. The former had a high case fatality ratio of 43 per cent while the latter had a much lower fatality (6.7%). The biphasic trend in fever was observed only among patients with hepato-renal involvement.

Table III shows the prevalence of various symptoms and signs among the two series of cases, the one reported by Taylor and Goyle (1931)[5] and the series reported by Singh *et al* (1999)[14]. The statistical significance of the difference in the prevalence was tested by χ^2 test and results of this are incorporated in the Table. Some of the symptoms and signs such as sudden onset, prostration, melena, bleeding gums, epistaxis, hiccough, splenomegaly, relapse of fever after a period of remission and albuminuria were not reported by Singh *et al*[14]. It is not clear whether the lack of mention about these symptoms/signs was due to absence of these in all patients in their series or because they did not record these. Similarly, some symptoms and signs were not reported by Taylor and Goyle[5]. Among the 10 symptoms/signs whose prevalence among the cases was reported by both the investigators, the presence of six was significantly different between the two case series. These were muscle pain and tenderness, vomiting, diarrhoea, haemoptysis, haematemesis and sub-conjunctival haemorrhage. The most noticeable difference was in the prevalence of haemoptysis. While it occurred in about 52 per cent of the case series of Singh *et al*[14], it was observed in only less than 10 per cent of cases reported by Taylor and Goyle[5]. The prevalence of two other bleeding manifestations *viz.* haemetamesis and sub-conjunctival haemorrhage was much lower in the 1929 case series. The prevalence of symptoms/signs such as muscle tenderness, conjunctival congestion and jaundice was lower in the case series by Singh *et al*[14] as compared to the case series by Taylor and Goyle[5].

It seems that both haemorrhagic manifestations and pulmonary involvement were much more common in the case series of 1996-1997[14] as compared to the case series of 1929[5]. One fatal case described in detail by Taylor and Goyle[5] had haemoptysis on the day of admission and another bout on the next day. Just prior to the death, the patient had a severe bout of haematemesis. The authors suggested that 'there was as a rule no evidence of respiratory complication'. However, they added that in severe cases there was evidence of acute bronchitis and reported that three fatal cases had bronchitis. It is not clear whether chest X-ray was available at Port Blair those days and, if available, whether or not these were obtained for the patients. The authors also mentioned that broncho-pneumonia or lobar-pneumonia was not discovered in any of the patients.

Autopsy findings reported by Taylor and Goyle[5] include sub-endocardial, sub-pleural and sub-peritoneal haemorrhages as well as congestion and bleeding in small and large intestines. There was no mention of

Table III. Prevalence of symptoms/signs among the case series reported by Taylor and Goyle (1931)[5] and Singh *et al* (1999)[14]

Sl. No	Symptom/sign	1929		1996		χ^2	*P*
		n	(%)	n	(%)		
1	Fever	64	100.0	58	100.0	--	--
2	Muscle pain and tenderness	61	95.3	48	82.8	5.04	0.0250
3	Conjunctival congestion	42	65.6	29	50.0	3.05	0.0810
4	Jaundice	42	65.6	30	51.7	2.43	0.1190
5	Vomiting	9	14.1	30	51.7	19.84	0.0000
6	Diarrhoea	5	7.8	14	24.1	6.17	0.0130
7	Hepatomegaly	6	9.4	4	6.9	0.03	0.8666
8	Haemoptysis	6	9.4	29	50.0	24.55	0.0000
9	Haematemesis	2	3.1	13	22.4	10.5	0.0012
10	Subconjunctival haemorrhage	2	3.1	17	29.3	15.87	0.0001
11	Sudden onset	63	98.4				
12	Prostration	61	95.3				
13	Melena	5	7.8				
14	Bleeding gums	3	4.7				
15	Epistaxis	1	1.6				
16	Hiccough	3	4.7				
17	Splenomegaly	5	7.8				
18	Relapse of fever	12	18.8				
19	Albuminuria	29	45.3				
20	Body ache			56	96.6		
21	Headache			54	93.1		
22	Rigor and chills			45	77.6		
23	Cough			41	70.7		
24	Breathlessness			25	43.1		
25	Oliguria			12	20.7		
26	Lung crackles			26	44.8		
27	Hypotension			23	39.7		
28	Neck stiffness			7	12.1		
29	Altered sensorium			7	12.1		

the lungs being filled with bloody fluid indicative of alveolar haemorrhage. It seems that haematemesis and melena were more ominous signs in their case series as 85 per cent of the cases who developed haematemesis or melena died as opposed to 50 per cent of those who developed haemoptysis.

Death apparently occurred at a later stage of the disease in the case series by Taylor and Goyle[5] as compared to that of Singh *et al*[14]. In the case series of Singh *et al*[14], 79 per cent of deaths occurred within 24 h of hospitalization and another 14 per cent of deaths occurred on the second day. Only one death occurred after 48 h of hospitalization. In contrast, in Taylor and Goyle's case series[5], eight of the 12 deaths (66.7%) occurred between 5th and 11th day of disease, two (16.7%) deaths each occurred before 5th day and after 11th day. Taylor and Goyle[5] reported day of disease when death occurred and Singh *et al*[14] reported day of hospital stay when death occurred. These two cannot be compared.

Severe pulmonary haemorrhage in leptospirosis

Severe pulmonary haemorrhage as a fatal and severe complication of leptospirosis was recognized in China and Korea[15]. A great deal of attention was paid to it in China where it was thought to be caused by a serovar called Lai of Icterohaemorrhagiae serogroup[21]. It became widely known after the outbreak of leptospirosis with pulmonary haemorrhage that occurred in Nicaragua following floods in 1995[17]. Severe pulmonary haemorrhage syndrome (SAPH) is now a well recognized severe and fatal complication of leptospirosis[22]. The case fatality ratio in SAPH could be more than 50 per cent in certain settings and it is presently considered as the prime cause of death in leptospirosis[23]. A case-control study done using population-based surveillance data in Brazil had shown that pulmonary involvement was the strongest predictor of mortality in leptospirosis with an odds ratio of 6.0[24]. Experience in some countries indicates that the incidence of SAPH is probably increasing during the past one and a half decades. In Salvador in Brazil, where an active surveillance did not detect even a single case of SAPH among 1,786 cases of leptospirosis identified during 1996 to 2002, it started appearing in 2003 and the number of such cases unexpectedly increased subsequently[23].

SAPH, also termed as severe pulmonary hemorrhagic leptospirosis (SPHL), severe pulmonary form of leptospirosis (SPFL) or leptospiral pulmonary haemorrhage syndrome (LPHS) is considered by some as a form of leptospirosis distinct from Weil's disease because pulmonary manifestations are found to occur independently without renal and hepatic manifestation or along with them[25]. Manifestations of SPHL include dyspnoea, lung crackles, radiographic findings of alveolar infiltrates and massive haemoptysis[26]. The most remarkable aspect of the clinical picture is profuse lung haemorrhage[27]. Although the patient may have normal arterial blood gases and normal chest X-ray initially, pulmonary haemorrhage, once sets in, can progress rapidly leading to dyspnoea, respiratory distress and frank haemoptysis when chest X-ray will show extensive bilateral interstitial infiltrate and areas of alveolar filling similar to those seen in viral pneumonia, bronchopneumonia, miliary tuberculosis, pulmonary haemorrhages and in adult respiratory distress syndrome[27].

Patients with SPHL usually have haemorrhagic lesions in various other organs, suggesting that SPHL might be the pulmonary manifestation of generalized haemorrhage[26]. The histology of the autopsy specimens of lung tissues of 21 cases died of leptospirosis with moderate to severe pulmonary haemorrhage in Sri Lanka showed extensive alveolar haemorrhages, hyaline like deposits, neutrophilic infiltrations, and swollen septa with congested blood vessels[28]. The histological findings were not indicative of secondary haemorrhages following disseminated intra-vascular coagulation (DIC) or isolated pulmonary injuries due to ventilation[28] although DIC is known to occur in leptospirosis[29,30]. Immunohistochemical studies of lung tissues of patients died of leptospirosis with pulmonary haemorrhage showed presence of fibrin aggregates and leptospiral antigen in the lumen, vascular endothelium and alveolar surface. The patients had thrombocytopenia, which was not due to DIC but due to activation, adhesion, and aggregation of platelets to the stimulated vascular endothelium, with an amorphous electron-dense substance between the endothelial cells and the adherent platelets[31].

The presence of leptospiral antigen in the lung indicated a direct action of the microorganism (or of its by-products) in the genesis of the tissue lesions[27]. Pulmonary haemorrhage usually occurs at an earlier stage of the disease than other organ involvement[14] indicating that pulmonary vascular injury probably is occurring during the leptospiraemic phase itself and suggests a direct role of the organisms in the causation of it. Corda *et al*[32] suggest that pulmonary pathology in SPHL is associated with unique histological patterns that differ from those of other causes of pulmonary haemorrhage and is characterized by the linear deposition of immunoglobulins (IgA, IgG and IgM) and complement on the alveolar surface, which may have a role in the pathogenesis of pulmonary haemorrhage in leptospirosis. This has been earlier observed in guinea pig model[33] and suggests a significant role of immune response in SPHL[26].

In China and Korea, pulmonary haemorrhage was thought to be a unique manifestation of infection with *Leptospira* serovar Lai. However, several genospecies and serovars of *Leptospira* have been shown to cause pulmonary haemorrhage[19]. Various virulence factors have been investigated for their role in the causation of pulmonary haemorrhage in leptospirosis. These include haemolysins, sphingomyelinase *sphA,* pore-forming protein *sphH*, the endothelial cell and erythrocyte membrane damage inducing protein *sph2,* surface exposed proteins *LigA, LigB* and *LigC* that contain bacterial immunoglobulin-like domains

indicating potential role as adhesins, laminin binding proteins *LenH*, *Lsa21, Lsa27, Lsa63* and the protein with peptidoglycan-binding motif *Loa22*[34]. *Loa22* was the first genetically described virulence factor of *Leptospira* and was demonstrated to contribute to the ability of *L. interrogans* serovar Lai to cause disease in hamsters and guinea pigs[26].

No specific host factor has been identified to be associated with development of SPHL except for a single report of association with HLA-DQ6[35]. Although a higher predilection of female patients to develop SPHL was reported from Brazil[23], this has not been observed in anywhere else. It affects all age groups including children. During the outbreaks of leptospirosis with pulmonary involvement in North Andaman[16], the most common age group of the patients was 5-9 years for males and 10-14 yr for females. Although previous exposure and seropositivity have been shown to reduce the severity of the disease[36], it is also possible that previous subclinical exposure to one serovar may increase risk of development of SPHL when infection with another serovar occurs similar to the occurrence of dengue haemorrhagic fever and dengue shock syndrome[26].

SPHL has emerged as a major public health concern in leptospirosis endemic regions. Since it usually runs an acute and fulminant course, there is only limited opportunity for medical intervention and prevention of mortality. Various treatment regimens such as pulsed corticosteroid therapy[37], immuno-suppresents such as methotrexate and cyclophosphamide[38] and plasmapheresis[39] have been tried, but the effectiveness is doubtful. In the recent years new insights into the pathogenesis of leptospirosis have been gained. Leptospiral virulence factors and pathogenesis are in the focus of attention of leptospirologists. Major research projects such as the project for sequencing the whole genomes of a large array of leptospiral strains will eventually lead to effective treatment strategies against SPHL.

Severe pulmonary haemorrhage – a historically overlooked complication of leptospirosis

The question whether SPHL in leptospirosis is a newly emerging phenomenon or was it occurring earlier also, remains unanswered. The detailed clinical description of a series of severe cases of leptospirosis by Taylor and Goyle[5] and later by Singh *et al*[14] from the same area gives an opportunity to analyse this issue. In India, its first recognition of SPHL came when the outbreaks of Andaman Haemorrhagic Fever, which was a syndrome of fever with pulmonary haemorrhage, was proved to be caused by *Leptospira*[16]. But from the preceding discussion of the case series reported by Taylor and Goyle[5] it was clear that pulmonary involvement was occurring in Andaman much earlier also, though its importance as determinant of mortality in leptospirosis might not have been known for various reasons.

Apparently the incidence of pulmonary haemorrhage during the 1920s was much lower than that is seen in 1990s and subsequently. There is a major factor that needs to be considered. Since severe pulmonary haemorrhage was not recognized as a potential complication of leptospirosis in 1920s, it is unlikely that cases presenting with pulmonary involvement but without typical signs of Weil's disease would have passed for a clinical diagnosis of leptospirosis and investigated. This would effectively exclude many cases of pulmonary involvement in the case series reported during that period. Once pulmonary involvement was recognized as a complication of leptospirosis, the clinical case definition of leptospirosis was made broader to include such cases also. Obviously, case series in this era are likely to include many such cases also. However, there is a possibility of a true increase in the incidence of pulmonary involvement in leptospirosis because of multi-factorial reasons relating to the causative agent, animal vectors or carries, environment and ecology or human host. The increase in the density and diversity of the animal vectors, a broadening of the range of circulating serovars, the interactions between the vector and the agent and host factors such as increasing exposure due involvement in rice or paddy cultivation or immunological phenomena are some of the possible reasons. The increased virulence of the agent through gene acquisition and gene loss on an evolutionary time scale and the resulting change in the gene content, gene order and gene expression cannot be ruled out.

Though the proportion of cases that developed pulmonary involvement was low in 1929, case fatality ratio in such cases was higher than that among cases that presented only with hepatic and/or renal involvement. The case fatality ratio among patients with pulmonary involvement, was higher in the 1929 case series as compared to the case series in 1996-1997. Cases with GI bleeding had an even higher CFR and when both pulmonary and GI involvements were present, the CFR was 100 per cent. X-ray facility

was probably not available at Andaman in those early days and, therefore, the nature of lung lesions in those who developed pulmonary involvement was not properly documented. Subpleural haemorrhages were observed during autopsy of fatal cases, but it is not clear whether or not the investigators looked for intra-alveolar haemorrhages. About a quarter of the patients who had prolonged exposure to stagnant water (bund construction workers) had haemorrhagic manifestations and two (11%) had pulmonary involvement, which is similar to the prevalence of haemorrhages and pulmonary involvement reported in many case series in recent years[14].

Globally, the reports of pulmonary involvement have been increasing during the past two decades. Since it was first noticed in China and Korea and later in Nicaragua and Andaman Islands, reports of occurrence of SPHL have been coming from many other countries. Because of the increased awareness about this condition, people might be paying more attention to it in leptospirosis endemic countries, leading to an apparent increase in the occurrence. However, the possibility of an *Leptospira* having acquired an increased virulence, and spread of such virulent strains from small foci to larger areas due to environmental changes and human and animal population dynamics or the host factors arising from social and demographic changes contributing to the apparent increase in the occurrence of SPHL cannot be ruled out. Whichever might be the attributable cause of the emergence of SPHL as the most important cause of mortality in leptospirosis, a closer look of the data presented by earlier researchers will show that pulmonary involvement in leptospirosis is not a new phenomenon, but was occurring ever since *Leptospira* was identified as the aetiology of Weil's disease.

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