LEPTOSPIROSIS: AN EMERGING HEALTH PROBLEM IN THAILAND

W Tangkanakul[1], HL Smits[2], S Jatanasen[1] and DA Ashford[4]

[1]Bureau of General Communicable Diseases, Department of Disease Control (DDC), Ministry of Public Health (MOPH), Nonthaburi, Thailand; [2]KIT Biomedical Research, Royal Tropical Institute/ Koninklijk Instituut voor de Tropen (KIT), Amsterdam, The Netherlands; [3]National Center for Infectious Diseases, Center for Disease Control and Prevention (CDC), USA

Abstract. Leptospirosis is an emerging health problem in Thailand, with dramatic increases in reported incidence since 1996. The annual number of reported leptospirosis cases increased from 398 cases in 1996 to 14,285 cases in 2000. In 2001, 2002, and 2003, the number of reported cases decreased, but still remained high at 10,217, 6,864, and 4,958 cases, respectively. The epidemiological characteristics of leptospirosis in Thailand include a peak incidence in September and October in association with the rainy season. A vast majority of the cases (90%) were reported in the Northeast region. The case fatality rate was as high as 4.4%, having a predominant association with male farmers aged 15 to 45 years. Outpatient cases were approximately 9 times more common than admitted cases, with an apparent recent shift in the pattern of infecting serovars among reservoir animals and humans.

INTRODUCTION

Thailand is situated in Southeast Asia from 5º 30´´ to 21º North latitude and from 97º 30´´ to 105º East longitude. The country is divided into 4 geographical regions: North, Central, South, and Northeast. There are three seasons in Thailand: cool, from November to February, hot, from March to May, and a rainy season from June to October. The average minimum temperature is 20ºC and the average maximum temperature is 37ºC. Thailand receives an average annual rainfall of about 1,700 mm or 252 billion m^3. Half of the country, mostly in the North and the Northeast, has fewer than 80 rain-days per annum.

Leptospirosis is a zoonotic infection caused by pathogenic spirochetes of the genus *Leptospira* (Faine, 1998; Tappero *et al*, 1998; Levett, 2001). Risk groups include veterinarians, cattle, rice, and sugarcane farmers, military personnel, meat workers, sewage workers, and garbage collectors. In addition, recreational activities are increasingly recognized as risk factors for leptospirosis, with outbreaks being reported among swimmers, white water rafters, triathletes, and adventure athletes (Jackson *et al*, 1993; CDC, 1998). Outbreaks of leptospirosis have been associated with conditions of flooding (Sanders *et al*, 1999).

This paper describes the epidemiological patterns of leptospirosis in Thailand and a recent increase in cases in Thailand. Reasons for the increased cases are discussed. Strategies for the assessment and control of leptospirosis are suggested.

EPIDEMIOLOGICAL PATTERNS

Leptospirosis in Thailand, 1942-1994

Leptospirosis was first reported in Thailand in 1942 by Yunibandhu *et al* (1943). In 1972, leptospirosis was included as one of the 58 reportable infectious diseases under the National Passive Surveillance System. Reported leptospirosis cases are based on the clinical case definition of the WHO. Information was collected on a standard case report form and reported to the Ministry of Public Health (MOPH).

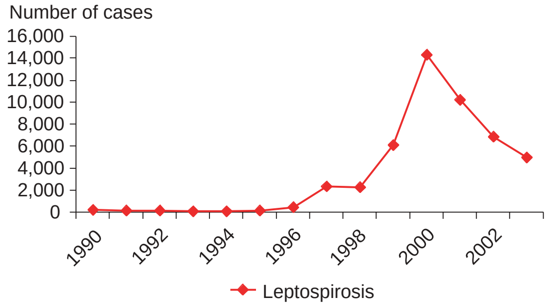
From 1972 to 1988, 10 to 20 leptospirosis cases were reported annually in Thailand. Be-

Correspondence: Dr Waraluk Tangkanakul, Bureau of General Communicable Diseases, Department of Disease Control, Ministry of Public Health, Nonthaburi 10100, Thailand.
Tel: 66 (0) 2590-3190-1; Fax: 66 (0) 2591-8432
E-mail: Waraluk@health.moph.go.th

tween 1982 and 1994, the number of cases ranged from 55 to 272 cases per year (Fig 1) and represented an annual incidence rate of approximately 0.3/100,000 population (MOPH, Thailand; Tangkanakul *et al,* 1998). From 1991 to 1995, around 34% of the cases were reported from the Northeast region. The disease showed a seasonal fluctuation with most of the cases occurring between June and December. The peak incidence was observed in October. Most leptospirosis cases were seen among farmers aged 15-45 years, with a male to female ratio of nearly 30:1 in some areas (Tangkanakul *et al*, 1998).

Common reported symptoms included fever, myalgia, headache, conjunctival suffusion, and meningism (Tangkanakul, 2000). The most common serious complications reported were jaundice and renal impairment. Case-fatality rates were around 10%. In early serological studies of leptospirosis patients, Icterrohaemorrhagiae and Bataviae had the greatest serologic reactivity by MAT (Yunibandhu, 1943; Adthamsoontorn *et al,* 1960; Sundharagiati *et al*, 1964; Charoonruangrit and Bunpacknavig, 1964; Bunnag *et al*, 1965; Nimmanitya *et al,* 1984). A serologic study comparing patients presenting with acute fever of unknown origin (FUO) suggested that leptospirosis represented between 20 and 40% of FUO cases in rural and urban hospitals (Bunnag *et al*, 1965; Jatinandana *et al*, 1971; Nimmanitya *et al,* 1984; Heisey *et al*, 1988; Sundharagiati *et al*, 1996). Bataviae and Pyrogenes represented the serovars with the highest immunoreactivity by MAT in those studies (Sundharagiati *et al*,1996; Heisey *et al*, 1988). In addition, seroprevalence studies of the general population performed in the early 1960's suggested a general seroprevalence of 28% in 71 provinces (Sundharagiati *et al*, 1964). Various serosurveys performed in the 1960's indicated that Bataviae, Icterohaemorrhagiae and Grippotyphosa had the greatest serologic reactivity by MAT in normal people (Adthamsoontorn *et al,* 1960; Charoonruangrit *et al,* 1964; Sundharagiati *et al*, 1964; Tangkanakul, 2000).

During the 1960s, some animal surveys were performed in order to help identify potential reservoirs for infection in Thailand. Rodent seroprevalence was estimated to be approximately 10% to 50% and leptospiral infections were found to be uncommon in house mice (Sundharagiati *et al*, 1969). In other studies, cultured leptospires from rat kidney tissue (*Rattus. norvegicus*) yielded an overall prevalence of 66%, suggesting that serosurveys may have been underestimating the prevalence in rodents (Sundharagiati *et al*, 1965). Serotyping of isolates showed that the serovars most common in rodents were Autumnalis, Bataviae, Javanica and Hebdomadis. These studies concluded that rodents were important reservoirs and sources of infections. However studies of seroprevalence in dogs captured in Bangkok showed a seroprevalence of 43%. In 8.1% of the dogs, leptospires (Bataviae, Javanica, and Ballico) could be isolated (Sundharagiati *et al*, 1965).



Source: Disease notification report. Ministry of Public Health, Thailand.

Fig 1–Reported cases of leptospirosis by year in Thailand from 1990 to 2003.

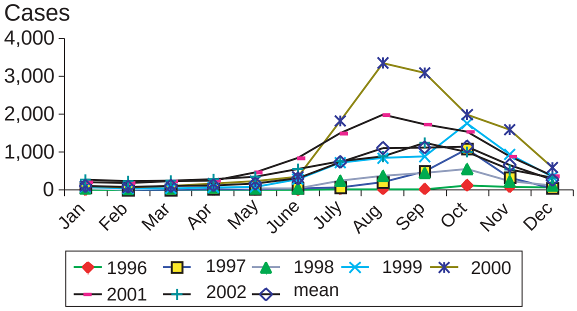
Leptospirosis in Thailand: 1995-2003

Data from disease notification reports indicated a drastically increase in leptospirosis cases between 1995 and 2003, with a peak in 2000. The number increased from 143 cases reported in 1995, to 398 in 1996, 2,331 cases in 1997, 6,080 cases in 1999, 14,285 cases in 2000, 10,217 cases in 2001, 6,864 in 2002 and 4,958 cases in 2003 (Fig 1). This was an increase in the incidence rate from less than 0.3 per 100,000 in 1995 to 23.7 in 2000, with a drop in subsequent years. There were 266 deaths reported in 1999 for a case fatality rate (CFR) of 4.4%, 362 deaths in 2000 for a CFR of 2.7%, 171 deaths in 2001 for a CFR of 1.7%, 95 deaths in 2002 for a CRF of 1.4%, and 82 death in 2003 for a CRF of 1.7 %. The male to female case ratio was 9:1 in 1995, 7:1 in 1996, 9:1 in 1997, 6:1 in 1998 to 1999 and 3:1 in 2000-2003 (MOPH, Thailand; Tangkanakul *et al,* 1998). As noted in the past, the peak incidence of leptospirosis still occurred in September to October each year (Fig 2).

Leptospirosis cases were seen in all age groups except in children younger than 5 years of age. A peak was observed in the age group 25 to 54 years, accounting for 80% of all cases. Each year, most cases were farmers (71.5-83.9%) aged more than 15 years. The average inpatient to outpatient case ratio during 1997-1999 was approximately 9:1. Pulmonary hemorrhage was observed as a major cause of death (Panaphut *et al,* 2002).

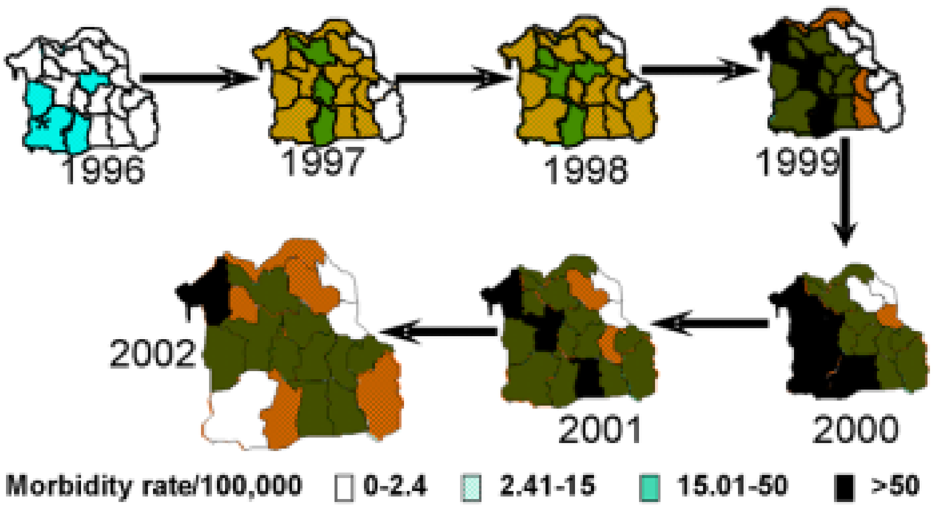
The epidemic began after flooding in 1996 in the Nong Bunnak district, Nakhon Ratchasima Province in the Northeast (Sthonsaowapak, 1997). In 1997, it expanded to 16 out of 19 provinces in the Northeast region. The epidemic extended to the North and the Central. By 1997 the epidemic had expanded to 37 provinces, continuing to spread to 57 provinces in 1998, and to 64 provinces in 1999 (Tangkanakul *et al,* 1998). In the year 2000, provinces adjacent to Cambodia and the Central regions showed a leptospirosis morbidity rate of more than 50 per 100,000 inhabitants (Fig 3).

High morbidity provinces were situated in the lower part of the Northeast, near the Cambodian border (Fig 3). Provinces with low morbidity were in the upper part, near the border with the Laos People's Democratic Republic. The average total rainfall in the lower part (1,000 - 1,500 mm per year) was less than in the upper part (1,400-2,000 mm per year). The many tributaries of the Shi and Nam Moon rivers divide large areas of the lower part. These areas are flooded during the rainy season, but are very dry during the rest of the year. The areas in the upper part are along Mekong River in the North.



Source: Disease notification report. Ministry of Public Health, Thailand.

Fig 2–Distribution of Leptospirosis cases by month in Thailand from 1996 to 2002.



Source: Disease notification report. Ministry of Public Health, Thailand.
(*)=Nakhon Ratchasima Province

Fig 3–Morbidity rate of leptospirosis by province, Northeast, Thailand between 1996 and 2002.

Serologic data from outbreak investigations in the late 1990s indicate that Bratislava, Sejroe and Pyrogenes have become the most common serovars (Chaifoo *et al*, 1998; Arjkien, 2000; Boonyod *et al*, 2001; Tangkanakul *et al*, 2002). This indicates a shift from the historical MAT data, which showed the predominant serovars as Icterohameorrhagiae and Bataviae (Yunibandhu, 1943; Adthamsoontorn *et al,* 1960; Charoonruangrit *et al,* 1964; Sundharagiati *et al*, 1964; Bonnag *et al*, 1965; Nimmanitya *et al,* 1984). During the spring of 1998, an outbreak of febrile illness occurred in the Kosum Phisai district, Maha Sarakam Province in Northeast Thailand after flooding (Ratanasang *et al*, 2001). A serosurvey using slide microscopic reaction (H.S *leptospira* antigen, Sanofi Pasteur) was conducted among 245 asymptomatic farmers and agricultural workers aged 15 to 65 years. The overall prevalence rate was 13.5% (male = 13.9% (22/158), female = 12.7% (11/87). The highest prevalence rate was found in the 20-24 age group (28.6 %), followed by the 40-44 age group (25%) (Ratanasang *et al*, 2002). This overall prevalence rate was higher than that found in normal male military personnel in Khon Kaen in the Northeast (8.13%; 30/369). The most frequent detected serovar by MAT in military personnel was Bratislava (Phulsuksombati *et al*, 2001a).

In 1998, a matched case-control study was conducted in Nakhon Ratchasima with the aim of identifying risk factors among rice field workers (Tangkanakul *et al*, 2000a). The results indicated that wading through stagnant water (OR 4.9, 95%CI 1.7 - 14.1), applying fertilizer in wet fields for more than 6 hours a day (OR 3.4, 95%CI 1.5 - 7.8), plowing in wet fields for more than 6 hours a day (OR 3.5, 95%CI 1.1 - 11.6), and pulling seedlings in wet fields for more than 6 hours a day (OR 3.1, 95%CI 1.02 - 9.3) were risk factors. Plowing, pulling seedlings and fertilizing activities were associated with a greater risk of skin cuts and abrasions than other rice farming activities. The seroprevalence rate in agricultural workers involved in high-risk activities was 42.9% (30/70) (Tangkanakul *et al*, 2000b). In 1999, an outbreak in the Buri Ram Province in the Northeast among villagers involved in pond cleaning was investigated. The villagers had been engaged in pulling reeds and water hyacinths from the water. Of 104 persons suspected of having leptospirosis, anti-leptospiral antibodies were detected in 43 (41%). The wearing of long pants or skirts during the pond-cleaning activities was found to be protective (OR 0.2; 95%CI 0.067-0.701), whereas the presence of more than two wounds on the body was found to be a risk factor (OR 3.9; 95%CI 1.6-10.2) (Phraisuwan *et al*, 2002).

Rodents have long been associated with leptospirosis in Thailand. In 1998, an assessment of rodent populations in Nakhon Ratchasima revealed a ten times greater density of rats in an epidemic subdistrict (1 rat/80 m^2) than in a non-epidemic subdistrict (1 rat/800 m^2). The isolation rate from the rat kidneys using EMJH medium (n = 218) in Nong Bunnak (epidemic subdistrict) was 5.5%. All positive rats were *Bandicota indica*. All rats (n = 132) from Nong Yang (non-epidemic subdistrict) were found to be uninfected. Monoclonal antibody testing indicated that 11 were serogroup Autumnalis and one Pomona (Tangkanakul *et al*, 2002; Phulsuksombat *et al*, 1999).

From June 1999 to September 2000, 989 rodents were captured from 4 epidemic provinces (Buri Ram, Surin, Khon Kaen and Kalasin) in the Northeast; 321 rodents were captured from a non-epidemic province (Nakhon Phanom) in the Northeast. Leptospires were isolated from rat kidney using EMJH medium. In the epidemic provinces, Leptospires were isolated from 7 out of 9 species of rodents (*Rattus norvegicus* (36.7%, 92/251), *Bandicota indica* (13.1%, 24/183), *Rattus losea* (7.7%, 5/65), *Rattus rattus* (7.1%, 9/126), *Rattus argentiventer* (6.2%, 6/97), *Bandicota savilei* (6.0%, 3/50), and *Rattus exulans* (1.0%, 2/199). In the non-epidemic province, Leptospires were found in 4 of 9 species, including *Rattus norvegicus* (62.5%, 35/56), *Bandicota indica* (14.6 %, 12/82), *Rattus losea* (16.7%, 1/6), and *Rattus rattus* (1.7%, 1/58). *Mus cervicolor* and *Mus calori* were not found to be reservoirs of leptospirosis (Phulsuksombati *et al*, 2001b).

The prevalence of leptospires in rodents in the epidemic provinces and the non-epidemic province was 14.3% (141/989) and 15.3% (49/321) respectively. The isolation rate from rice field rats was 9.0% (47/521) and 9.5% (14/148) in the epidemic and non-epidemic provinces, respectively, whereas from house rats the prevalence was 20.1% (94/468) and 20.2 (35/173) in the epidemic and non-epidemic provinces, respectively. The total infection rate of leptospirosis in rodents was 14.5% (190/1310). Leptospiral isolates were identified from a panel of 26 standard antisera from a cross agglutination absorption test (CAAT) at the WHO/FAO Leptospirosis Reference Laboratory, Brisbane, Australia. *Rattus norvegicus* was the major reservoir of serogroup Pyrogenes, whereas *Bandicota indica* was infected with Autumnalis, Bataviae, Pyrogenes, Javanica and Australis serogroups. Our study failed to find a difference in the total population of rodents between the epidemic and non-epidemic provinces (Phulsuksombati *et al*, 2001b).

Serosurveys among a variety of other animals species during 1999 did not find any significant difference in seroprevalence between the 4 epidemic provinces (Buri Ram, Surin, Khon Kaen, Kalasin in the Northeast) and a non-epidemic province (Nakhon Phanom in the Northeast). The prevalence of antibodies found using MAT in epidemic provinces was 77.2% (179/232) in cattle, 86.1% (155/180) in buffalo, and 60.4% (58/96) in swine. The prevalence of leptospiral antibodies in the non-epidemic province was 69.85% (90/129) in cattle, 82.2% (88/107) in buffalo and 62.5% (40/64) in swine. In cattle and buffalo, seroreactivity was observed mainly with serogroups Sarmin, Ranarum, Sejroe and Castellonis. In swine, reactivity mainly was observed with serovars Sarmin, Ranarum, Bratislava and Pomona (Suwancharoen *et al*, 2000).

DISCUSSION

Leptospirosis was first reported in Thailand 62 years ago. The incidence has dramatically increased since 1996, with a peak in 2000. During this period, leptospirosis showed the same seasonal variations, and affected the same high-risk groups, mostly agricultural workers, affected before the onset of the epidemic. There are areas that deserve attention, such as: 1) the center of the epidemic is in the Northeast, 2) the ratio of male to female cases decreased, 3) a shift in the predominant infecting serovars, and 4) a change in the most common complications.

Reported leptospirosis cases were based on the initial clinical diagnoses of the physicians. Variation in the experience and awareness of the physicians regarding leptospirosis can lead to case ascertainment bias in both over- (false positive) and under- (false negative) diagnosis. Due to the protean nature of the disease, leptospirosis cases in Thailand can present and be reported as FUO or scrub typhus. In Thailand, the morbidity rate of FUO cases has increased from 239 in 2000 to 434 per 100,000 population in 2001. During 1996-2002, around 48% of reported FUO cases in Thailand were reported from the Northeast. Half of the FUO reported cases were farmers. The number of reported scrub typhus cases increased, with 1,210, 2,604, 1,969, 2,597, 3,914, 5,090 and 4,120 reported cases from 1996 to 2002, respectively (Tangkanakul and Ratanasang, 2003). Most causes of fever of unknown origin, such as leptospirosis, can not be identified, due to the limitation of laboratory diagnosis. Thus, the actual incidence of leptospirosis is not yet fully known. It cannot be said with any certainty whether the recent decrease in the number of cases marks the end of the epidemic or whether the epidemic is still expanding.

The cause and trigger factors of the epidemic are still unknown. The most likely reasons for the epidemic are: 1) climatological and ecological conditions in the Northeast, favor the transmission of the disease during the rainy season, 2) the changing ecology and epidemiology of domestic animals and changes in the agricultural practices in the Northeast, 3) increase in rodent density resulting in an increased risk of infection, 4) physicians and villagers have increased their awareness and ability to recognize the disease and seek health care, and an increase in the availability of laboratory testing, 5) the increase may be due to an associated shift in the predominant infecting serovars. The serological data indicating the change in circulating serovar, however, must be interpreted with caution. The analyses have been based on MAT data, which is unable to identify specific serovars responsible for infection, but rather represents a pattern of cross-reactivity among serovars represented in the testing panel. The high seroprevalence rates in the humans and animals observed in the early days of leptospirosis in Thailand may suggest that leptospirosis always has been a potential, but until recent years unrecognized and underreported, health problem.

To improve the surveillance data on leptospirosis in Thailand, laboratory confirmation of leptospirosis is essential. In recent years, a latex agglutination assay produced in Thailand has been implemented and is presently available at various sites at the district level (Naigowit *et al*, 2001). A confirmatory evaluation of the screening assay, however, is still needed to assess the validity of the test in hospital and field studies. Systematic evaluation of the current surveillance system is needed in order to ascertain current reporting practices among health care providers, to estimate the true burden of disease by laboratory confirmation, and to review the ability of the surveillance system to truly reflect the incidence of disease.

Confirmation of cases and epidemiological investigations linking outbreaks to sources of infection preferably should be done by MAT. MAT confirmation is limited to the National Institute of Health (NIH), Bangkok, and several regional laboratories, each serving 10-12 provinces. The Thai MAT incorporates 16 common serovars in its battery for the regional laboratory center and 23 serogroups for the NIH laboratory. Patterns of utilization of MAT confirmation among suspected leptospirosis cases in Thailand are presently unknown, and a reliable method of linking laboratory confirmation with epidemiological information is not currently in place.

Recent animal serosurveys conducted in an attempt to determine an animal reservoir have yielded mixed results, and as yet a plausible animal reservoir has not been identified. An encompassing effort to obtain serovar information from likely animal reservoirs, determined on the basis of regional epidemiologic information, is needed to address this issue. Identification of matching serovars, from both culture-confirmed human cases and prospective infecting animal reservoirs, is the most reliable method for identifying potential reservoirs, and a focused attempt to identify such a linkage is needed in Thailand.

A number of interventions were implemented in order to reduce the incidence of leptospirosis among rice farmers in the Northeast. These included advising the use of boots and gloves during farming work, and large rat extermination campaigns. Boots have been provided to local rice farmers for barrier protection, however, the effectiveness of this campaign has yet to be evaluated. Despite these interventions, the number of reported cases in the Northeast has not seemed to decrease. There are several possible reasons for this, they include the ineffectiveness of the implemented interventions, noncompliance with barrier protection methods, misguided eradication of animals other than the true reservoir, and as an artefact of changing reporting practices.

The economic impact of leptospirosis in Thailand, and the potential cost to benefit ratio of interventions have been incompletely analyzed, and the overall economic impact of leptospirosis has not yet been studied in great detail. Based on estimates of costs made in a community hospital, the medical care cost for a mild case is 1,800 baht (US$50) per case; for more severe cases, which require hemodialysis, the cost increases to 10,000 baht (US$278) (Sthonsaowapak, 1997). The economic impact on an individual, related to medical and nonmedical costs, was 2,790 (US$ 70.50)-24,700 baht (US$ 625.30) per case. Such a loss excluded the cost incurred by the public (Pornsiripongse *et al*, 2001). Other costs, such as the loss of workdays and cost of transportation for patients to and from clinical care are not included in this estimate.

For successful control, the passive surveillance system should be strengthened, and strategies for active surveillance in animals and humans should be developed and implemented. This surveillance should include improved techniques for culturing and identifying serovars infecting humans and animals. Through the identification of risk factors and identification of infecting animal reservoirs, effective methods of prevention and control may be designed. Control measures could include the escalation of barrier protection measures, vaccination and treatment of livestock, control of animals serving as infecting reservoirs, and increased sanitation measures. Ideally, these measures should also undergo thorough cost-effectiveness analysis. Education programs to alert people to avoidable and modifiable risk factors are in place and should be continued aggressively.

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