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Epidemiology, Surveillance and Laboratory Diagnosis of Leptospirosis in the WHO South-East Asia Region

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1. Introduction

Leptospirosis is a serious spirochete zoonotic disease of increasing worldwide prevalence and distribution (Bharti et al., 2003; Levett, 2001). The disease especially occurs in tropical areas with high rainfall and severe human cases may cause multi-organ failure leading to death. The World Health Organization (WHO) has estimated that approximately 10-100 cases per 100,000 people are infected annually in tropics (WHO, 2003). Although leptospirosis has been recognized for many years, it is considered a re-emerging disease of humans in many regions, exemplified by recent outbreaks in Brazil (Romero et al., 2003), India (Chaudhry et al., 2002), Malaysia (Sejvar et al., 2003), Nicaragua (Ashford et al., 2000; Trevejo et al., 1998), Sri Lanka (Epidemiology Unit-Sri Lanka, 2009a) and Thailand (Thaipadungpanit et al., 2007). It also causes substantial domestic livestock losses annually (Faine et al., 1999).

The disease occurs mainly in areas where humans or other animals come into contact with the urine of infected animals or a urine-polluted environment. Secondary human-to-human transmission occurs rarely (WHO, 2003). In tropics, approximately 10% of hospital admissions case attributes to leptospirosis infection, particularly following rains or floods (Kenneth et al., 2010). True incidence of leptospirosis is under-estimated due to lack of appropriate diagnostic capacity, and case finding and reporting in both human and veterinary medicine have been limited and biased (Cachay and Vinetz, 2005).

The clinical diagnosis of leptospirosis is complicated due to the varied and non-specific manifestations of its symptoms which resemble those of other infectious diseases in tropics, such as dengue fever or dengue hemorrhagic fever, malaria and scrub typhus. Inadequate and poor laboratory facilities tend to hamper the accurate identification of leptospirosis, thus the disease remains largely under-diagnosed and therefore under-estimated (WHO, 2003).

At present, 26.5 % of the 6.8 billion (2010) of the world population live in the WHO South-East Asia (WHO SEA) Region and 57% of the 774 million workforce is engaged in agriculture (WHO, 2009a). In the last few decades, tropical diseases continue to have crippling effects on the inhabitants especially people who live in poverty. The WHO SEA Region possess a high burden of tropical diseases such as lymphatic filariasis, soil transmitted helminthiasis, visceral leishmaniasis, trachoma, yaws, schistosomiasis, dengue, rabies, leprosy, Japanese encephalitis and leptospirosis, which are reported from one or more of the Member States of this region (Table 1) (WHO, 2011). The WHO SEA Region is a hotspot for emerging infectious diseases especially zoonoses and vector-borne diseases. Continuous population growth, mobility, rapid urbanization, environmental changes, deforestation, and climate change are acting as major factors that lead to increase the infectious diseases incidence in the region.

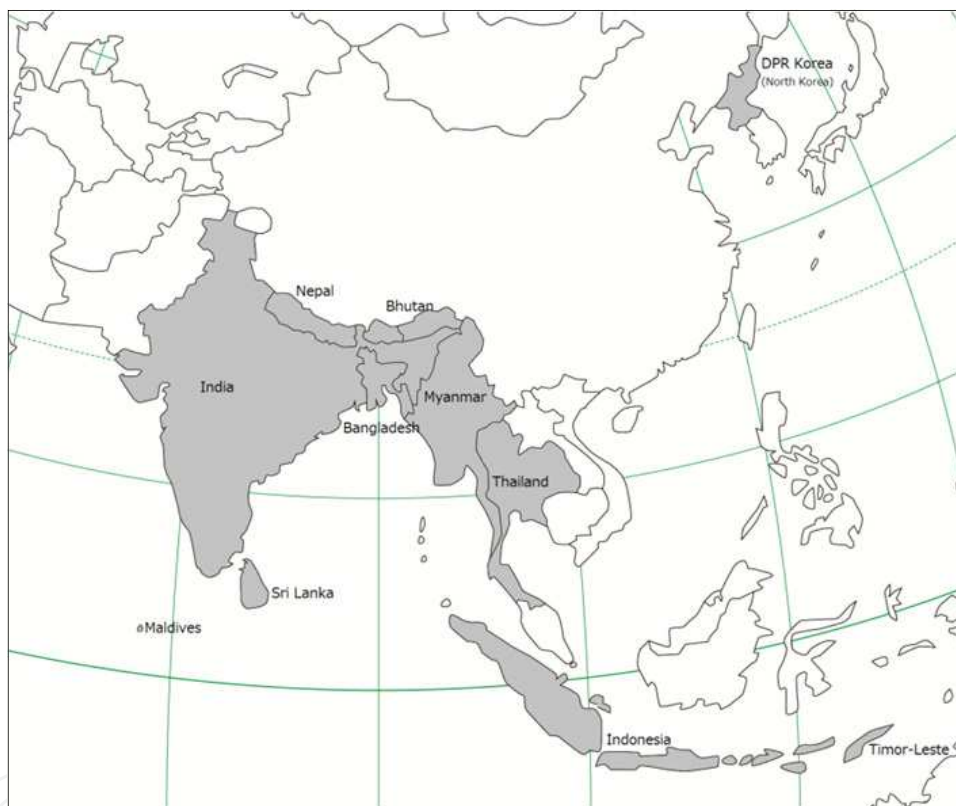


Fig. 1. Map of the WHO South-East Asia Region. The WHO South-East Asia (SEA) Region has eleven Member States: Bangladesh, Bhutan, Democratic People's Republic (DPR) of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor-Leste.

Despite the high prevalence of many infectious diseases in the region, up-to-date information is not sufficiently available to make an estimation of the burden of diverse diseases and any cross-country comparison difficult. Laboratory diagnosis and surveillance are crucial to generate proper epidemiological information on the diseases in a country or a region (WHO, 2002). However, most of the Member States are lacking proper diagnostic laboratories despite the continuation of endemics of these diseases for many decades.

The aim of this chapter is to summarize the current situations of epidemiology, surveillance and laboratory diagnosis of leptospirosis in the WHO SEA Region. We reviewed the

literature for the past two decades published in the PubMed (NLM) database. The combination of keywords <Country name> and <Leptospirosis> were used as search criteria. Appropriate publications were selected and summarized in subsequent sections. Furthermore, we used the Google search engine to locate the documents on leptospirosis of the WHO SEA Region.

Disease Name	Member country name										
	Bangladesh	Bhutan	DPR Korea	India	Indonesia	Maldives	Myanmar	Nepal	Sri Lanka	Thailand	Timor-Leste
1 Chikungunya				◆	◆	◆	◆		◆		
2 Dengue	◆	◆		◆	◆	◆	◆	◆	◆	◆	◆
3 Japanese Encephalitis				◆	◆		◆	◆	◆	◆	
4 Leprosy	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
5 Leptospirosis	◆			◆	◆			◆	◆	◆	
6 Lymphatic filariasis	◆			◆	◆	◆	◆	◆	◆	◆	◆
7 Rabies	◆	◆		◆	◆		◆	◆	◆	◆	
8 Schistosomiasis					◆						
9 Soil Transmitted helminthiasis	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
10 Trachoma				◆			◆	◆			
11 Visceral Leishmaniasis	◆	◆		◆				◆			
12 Yaws				◆	◆						◆

(Adopted from Communicable Disease Newsletter, World Health Organization Regional Office for South-East Asia January 2011 Volume 8 issue 1; and revised accordingly leptospirosis situation in the WHO South-East Asia Region, World Health Organization Regional Office for South-East Asia)

Table 1. Distribution of reported tropical diseases in South-East Asia region.

2. Epidemiology

Leptospirosis is an important public health problem in resource-poor countries in tropics. In tropical regions, cases are reported year-round but predominantly during the rainy season (Sarkar et al., 2002; Trevejo et al., 1998). The increased risk during the rainy season becomes higher after flooding that accompanies natural disasters, when the human population may be exposed to water contaminated with urine from infected animals. Outbreaks associated with flooding and natural disasters have occurred in Nicaragua in 1995 (Trevejo et al., 1998), in Brazil in 1996 (Barcellos & Sabroza, 2000), and in India in 2002 (Karande et al., 2002). Seasonality of leptospirosis would be related to agricultural cycles.

It has been shown that people who are engaged in agriculture and animal husbandry have high risk of leptospirosis in comparison to other occupations (WHO, 2011a). A case-control study in Thailand revealed an increased risk of leptospiral infection among persons that performed various agricultural activities in wet fields for > 6 hours/day (Tangkanakul et al., 2005). In tropical areas such as SEA Region, annual incidence rates ranges from 10-100 per 100,000 people (WHO, 2003) and the disease is endemic in almost all Member States for many decades. Recent outbreaks were reported from Sri Lanka, India and Thailand. Epidemiology of leptospirosis in SEA Region mainly depends on various socio-cultural, occupational, behavioral and environmental factors. Unfortunately, national incidence data is not available other than outbreak reports or research based case series studies in many SEA Member States (Table 2). Among the Member States, Bangladesh, Bhutan, DPR of Korea, Maldives, Myanmar, Nepal and Timor-Leste has limited or no published

epidemiological information compared to Thailand, Sri Lanka, India and Indonesia (WHO, 2008). In SEA region, the most recent large leptospirosis outbreak occurred in Sri Lanka in 2008, with 7,423 clinically diagnosed leptospirosis cases (Incidence rate 35.7 per 100,000 people) and 207 deaths reported according to leptospirosis case definition (Epidemiology Unit-Sri Lanka, 2009b). Although the number of leptospirosis cases and deaths were reduced in 2009 and 2010, Sri Lanka still reported the highest annual leptospirosis cases among the SEA Member States (4,980 in 2009 and 4,545 cases in 2010). Based on hospital-based sentinel surveillance data, nearly half of the cases are aged between 30-49 years and 80% are male. Two thirds of the patients were exposed to paddy fields and muddy areas either accidentally or due to the nature of occupation. During the 2008 outbreak, 37% of 1,414 clinically diagnosed cases were positive for genus specific MAT using the Patoc strain of *Leptospira biflexa*. Agampodi et al (2011) and Koizumi et al (2009) have investigated portions of the 2008 outbreak serum samples by MAT using a panel of pathogenic strains. The results revealed that serogroups Pyrogenes and Sejroe were predominant in Kegalle and Kandy, respectively.

Leptospirosis is an important public health issue in Thailand. From 1995 to 2000, the disease incidence rate increased from 0.3 to 23.7 per 100,000 people, although the incident rate has dropped in recent years (2009a). In 2009 Bureau of Epidemiology Department of Disease Control, Ministry of Public Health Thailand reported that 5,439 leptospirosis cases and 64 deaths due to leptospirosis (incidence rate of 8.57 per 100,000 people and fatality rate of 0.1 per 100,000 people) with the male to female ratio of 4:1. Of the 5,439 cases, 72.9% were aged between 25 - 64 years and 72.4% were occupied in agriculture and labor sectors. Most infections occur in agricultural workers, primarily rice producers (Bureau of Epidemiology Department of Disease Control, 2009).

In India, outbreaks of leptospirosis have increasingly been reported from the coastline: Gujarat (Clerke et al., 2002), Mumbai (Karande et al., 2002), Kerala (Kuriakose et al., 2008), Chennai (Ratnam et al., 1993) and Andaman Islands (Sehgal et al., 1995). A 5 year consecutive sero-epidemiological study conducted in Kerala state has shown that 29.6% inhabitants possessed anti-leptospiral antibodies and the prevalent serogroups were Autumnalis, Louisiana, Australis, and Grippotyphosa (Kuriakose et al., 2008). In another study conducted by Sehgal and colleagues as part of a multi-centric study on disease burden due to leptospirosis (initiated by the Indian Council of Medical Research in 2000), 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 possess anti-leptospiral IgM. 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. (Sehgal et al., 2003).

In Indonesia, human leptospirosis cases were reported first in 1952, when it had been known as Canicola fever (Smit et al., 1952). There was a marked increase in human leptospirosis cases between 2003 (85 cases) to 2007 (666 cases). The outbreak in 2007, approximately 93% of the cases were laboratory confirmed and the case fatality rate was 8% (WHO, 2009a). However, a recent outbreak in Bantul regency in Indonesia's central Java region had a 27% case fatality (Netnewspublisher, 2011). Prevalence of rickettsioses and leptospirosis was investigated among urban residents in Semarang, revealing that 13 out of 137 febrile patients were confirmed as leptospirosis (Gasem et al., 2009).

Although data on leptospirosis in Bangladesh is limited, LaRocque R. C., et al. (2005) reported 18% of dengue-negative febrile patients at two Dhaka hospitals were positive for leptospirosis by PCR in a 2000 dengue outbreak. In a serosurvey conducted in rural Bangladesh in 1994 revealed high prevalence of anti-leptospiral antibodies among both patients with jaundice and healthy controls (Morshed et al., 1994).

There is no published information on human leptospirosis in Bhutan and Myanmar. However, leptospirosis in animal populations has been reported from both countries (WHO, 2009a). In 2000 Maldives reported their first human leptospirosis case (WHO, 2009a). In Nepal, no national surveillance program for leptospirosis exists. However, Myint, K. S., et al (2010) detected anti-leptospiral antibodies in military personnel participating in an efficacy study of a hepatitis E virus vaccine in Nepal. Among the 1,566 study volunteers, the prevalence of leptospirosis was 9% among hepatitis cases and 8% among febrile cases. The predominant serogroups were Bratislava, Autumnalis, Icterohaemorrhagiae, and Sejroe. Timor-Leste and DPR Korea have no published data about human leptospirosis.

Considering the urgent necessity of obtaining proper and up-to-date leptospirosis burden data to formulate and revise ongoing control and prevention activities, the WHO convened an international consultation to assess potential methods to determine a global burden of leptospirosis in October 2006. As an outcome of this meeting, the Leptospirosis Burden Epidemiology Reference Group (LERG), established in partnership with other international organizations, has started conducting global research that provides the necessary data for designing an appropriate policy targeted towards decreasing the burden of leptospirosis. LERG conducted an informal expert consultation on surveillance, diagnosis and risk reduction of leptospirosis in SEA Region, in Chennai, India on 17-18 September 2009. The experts recommended necessary measures to improve surveillance, estimation of burden of the disease, advocacy, awareness and education, diagnosis and vaccination (WHO, 2009b). Although WHO's LERG mainly focuses on human leptospirosis and its burden, future models which estimate the burden of the disease should pay attention to animal reservoirs, climate change and other environmental factors that may have an effect on particular regions of the world (Abela-Ridder et al., 2010)

3. Surveillance systems

Disease surveillance is a critical component of the health system in generating essential epidemiological information for a cost-effective healthcare delivery (WHO, 2002). Through surveillance, incidences and distributions of diseases (e.g., leptospirosis) and the implications for effective public health strategies are identified. Although surveillance of leptospirosis has been in place in many SEA Member States for decades now, it has yet to be adopted and implemented as a monitoring tool to address issues related to control and prevention of the disease (WHO, 2002). Surveillance of leptospirosis has been proven to be an effective and economical disease control tool in detecting and preventing large outbreaks (Jena et al., 2004). The WHO provides standards and guidelines for leptospirosis surveillance (WHO, 1999). Only a few SEA Member States adopted these standards (e.g., Sri Lanka and Thailand). Most of the Member States are lacking specific government policies and legal frameworks to support surveillance and have inadequate laboratory facilities and reporting systems. Furthermore, there is poor interaction between human and veterinary health sectors for better coordination and collaboration toward surveillance and control of leptospirosis (Narain and Bhatia, 2010).

surveillance for leptospirosis. The sentinel surveillance seeks to obtain clinical (e.g. signs and symptoms), epidemiological (e.g. exposures), laboratory (e.g. infected serogroup) and prophylactic treatment (e.g. use of antibiotics) information among those suspected of having an infection (Epidemiology Unit-Sri Lanka, 2009a).

Surveillance of leptospirosis and other 49 diseases is currently (2009) undertaken in Thailand by the Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health. The disease surveillance data such as morbidity rate, mortality rate, gender, age group, occupation, place of treatment and type of patient (for death and cure cases) are published weekly and annually through the homepage of Bureau of Epidemiology, Thailand (<http://www.boe.moph.go.th/>).

Leptospirosis is one of the most economically important diseases in the livestock sector and possesses a zoonotic hazard towards the people who are involved in this sector. However, leptospirosis is drastically neglected in most of the WHO SEA Member States, although its surveillance in rodents and domestic animals is important for developing its appropriate control and prevention strategies. It is not a priority disease in the veterinary sector and there is no systematic surveillance among livestock in the WHO SEA Region. Furthermore, there is no veterinary and medical institutional arrangement to estimate the burden of leptospirosis in most of the Member States of the WHO SEA region.

4. Laboratory diagnosis

Leptospirosis has diverse clinical manifestations that resemble many other tropical infectious diseases such as dengue fever, malaria, and scrub typhus which are prevalent in the region. Though a large number of fever of unknown origin are reported to the health facilities, investigation for leptospirosis is not carried out partly due to poor knowledge of clinical manifestations of the disease or lack of proper laboratory diagnostic facilities. Thus a large number of leptospirosis cases are reported without laboratory confirmation which directly affects the estimated disease burden in the region. Laboratory diagnosis of leptospirosis involves two groups of tests. One group is designed to detect anti-leptospiral antibodies, while the other group is to detect leptospire, leptospiral antigens, or leptospiral nucleic acid in body fluids or tissues (Levett, 2001). Culture and microscopic agglutination test (MAT) are the gold standard methods for its laboratory diagnosis. However, these methods are laborious for the routine use.

The MAT is the most widely used diagnostic serological test. Although MAT detects serogroup-specific antibodies, it appeared to be of little value for predicting infecting serogroup (serovar) of patients (Levett, 2003; Katz et al., 2003; Smythe et al., 2009). MAT requires paired sera for definitive diagnosis of leptospirosis. Seroconversion or at least fourfold increase in the titer must be observed between acute and convalescent serum samples. Anti-leptospiral antibodies detected by MAT are present for months to years after infection. Thus, it is difficult to confirm acute infection from a single serum sample. In endemic areas, a high titer of 400 or more in a symptomatic patient is generally accepted as a criterion for disease confirmation (Levett, 2001). Furthermore, MAT requires maintenance of a panel of *Leptospira* cultures prevalent in a particular geographical area, and appropriate quality control must be employed.

Several whole *Leptospira* cell-based rapid screening tests for antibody detection in acute infection have been developed, including enzyme linked immunosorbent assay (ELISA),

latex agglutination test, lateral flow assay, and IgM dipstick (Bharti et al., 2003; Levett, 2001; McBride et al., 2005, Toyokawa et al., 2011). These assays have been used as alternatives to MAT but have low sensitivity especially during the acute phase (Smits et al., 2001; Effler et al., 2002; Hull-Jackson et al., 2006; McBride et al., 2007). Furthermore, the diagnostic accuracies of these techniques are poor in some areas where leptospirosis is endemic (Blacksell et al., 2006; Myint et al., 2007).

PCR is demonstrably useful for early diagnosis of leptospirosis before its antibody production has commenced. PCR protocols for detection of leptospiral DNA in clinical materials have been developed (Ahmed et al., 2009). Conventional or real time PCR assays targeting a range of genes, such as 16SrRNA, 23SrRNA, LipL32, LipL21, RpoB, GyrB, OmpL1, LigA and B, and flagellin, have been described (Slack et al., 2006; Stoddard et al., 2009; Reitstetter et al., 2006; Kawabata et al., 2001). However, PCR may not be widely applied in resource-poor countries due to its high operational cost (Sehgal et al., 2003). Thus, diagnostic methods that not only have higher sensitivity and accuracy for early-phase leptospirosis but also are applicable widely in resource-poor countries remain to be developed.

Country* (reference)	Area	Study duration	No of study participants	Diganostic methods used	Point prevalence	Demographics	Rsik factors	Prevalent serogroup
India (Chauhan et al., 2010)	Sub-Himalayan state of North India (i.e. Himachal Pradesh)	August 1 - October 31, 2009	13 leptospirosis suspected patients	IgM ELISA and PCR (G1 and G2 primers)	10 were IgM positive, One positive by PCR	Male: 77% Age: ranged 24-78years, mean 44years old	Contacted with animals or contaminat ed water	NA
Sri Lanka (Agampodi et al., 2011)	Kandy, Kegalle and Matale districts	August 20 2008 - January 6 2009	Of 746 patients with acute febrile illness 401 probable cases of leptospirosis were examined	ELISA, MAT and PCR	NA	NA	NA	Pyrogenes, Javanica, Sejroe and Hebdomadis
Indonesia (Gasem et al., 2009)	Semarang in central Java	Feb 2005 - Feb 2006	137 acute undifferentiated fever patients	Lepto Tek Dri Dot (a commercial prodcut), MAT and IgG ELISA	10%	NA	NA	Bataviae
Thailand (Wuthiekanu n et al., 2007)	9 provinces located in north, northeast, central and southern regions	March 2003 - November 2004	700 leptospirosis suspected patients	MAT and culture	20% were laboratory confirmed leptospirosis patients	Among confirmed cases median age was 35 years (range 10-68 years). 85% were men.	NA	Autumnalis, Bataviae, Pyrogenes, Javanika, Hebdomadis, Grippotyphosa
Bangladesh (Kendall et al., 2010)	Kamalapur, Dhaka	Jan 1 - Dec 31, 2001	878 febrile patients. Only 584 had paired sera samples	Sceening by IgM ELIA. Confirmation by MAT	8.4% (definite + probable infection)	Male 41% Age: 17.8+- 13.1 years		Sarmin and Mini
Nepal (Myint et al., 2010)	Army unit stationed in Kathmandu	July-August 2001	2000 volunteers from the Nepalese Army	IgM ELISA and MAT	9% among clinical hepatitis cases 11% among non hepatic febrile cases	All male, mean age (+-SD) 25.2+-6.25	NA	Bratislava, Icterohaemorrhagia e, Autumnalis and Sejroe

*No publication were found from Bhutan, DPR Korea, Madives Myanmar and Timor-Leste for the period of January, 2009 – October, 2011.

Table 2. Leptospinosis in WHO South-East Asian Member States bases on the publucation published form 2007 to 2011.

Inadequate and poor laboratory facilities available in the WHO SEA Region, tend to hamper the accurate identification of leptospirosis, thus remaining largely under-diagnosed and therefore under-estimated (WHO, 2003). Among the WHO SEA Member States, only India, Indonesia, Sri Lanka and Thailand have fully or partially implemented laboratory facilities to diagnose leptospirosis (WHO, 2009b). However, those laboratories need to be

strengthened and standardized to produce countrywide services and to perform more accurate and specific diagnostic procedures.

In Sri Lanka, two governmental institutions, namely the Medical Research Institute (MRI), the Ministry of Health and the Veterinary Research Institute (VRI), Department of Animal Health and Production, have the capacity to diagnose leptospirosis using MAT. However, MRI is capable of a limited genus level serological diagnosis using only *L. biflexa* Patoc I strain (Dassanayake et al., 2009). In 2008, 37% of 1,414 suspected leptospirosis human cases were serological positive, but no information on infective serogroup was available (Epidemiology Unit, Ministry of Health, 2009a).

In India, the isolation of pathogenic leptospires from human and animal hosts in several parts of India has been reported (WHO, 2006). Because there are only limited facilities for serotyping in the country, most of the isolates were typed to the serogroup level only (Gangadhar et al., 2008).

Diagnosis of leptospirosis in Indonesia has been performed at the Pasteur Institute located in Ho Chi Minh (HCM) City, Vietnam (Laras et al., 2002). In-house developed ELISA, MAT and PCR methods are employed in Thailand (Kee et al., 1994; Tangkanakul et al., 2005). In Thailand, local institutes collaborate with the Collaborating Center for Reference and Research on Leptospirosis, Brisbane, Queensland, Australia (Wuthiekanun et al., 2007).

5. Conclusion

Leptospirosis is an emerging zoonotic disease of public health importance in countries of the WHO's South-East Asia Region. In some Member States, the disease has been endemic for many decades and causes sporadic outbreaks. The disease epidemiology is tightly linked to regional climatic factors and major occupational sectors such as agricultural and livestock workers. Interventions need to give special attention to at-risk geographic areas with a high case fatality rate and to individuals of particular socio-demographic characteristics (*e.g.*, men and agricultural workers). Further research needs to be carried out concerning more pathophysiological information of the disease to prevent leptospirosis deaths that could be prevented with proper and timely treatment after an early and accurate diagnosis of the disease. However, adequate laboratory tests for early diagnosis are still lacking (Toyokawa et al., 2011). Diagnostic methods that not only have higher sensitivity and accuracy for early-phase leptospirosis but also are applicable widely in resource-poor countries need urgently to be developed. The existence of large numbers of reservoir animals and route of disease transmission make activities in prevention and control of leptospirosis in WHO SEA Region difficult, especially with financial constraints. The quality of data on which the control and prevention of leptospirosis in the region is based will hinge upon a periodic assessment of the efficacy with which the sentinel surveillance system captures, analyzes and disseminates information. Data quality along with accurate results from laboratory investigations will determine the true burden of leptospirosis infection in each member country and the region.

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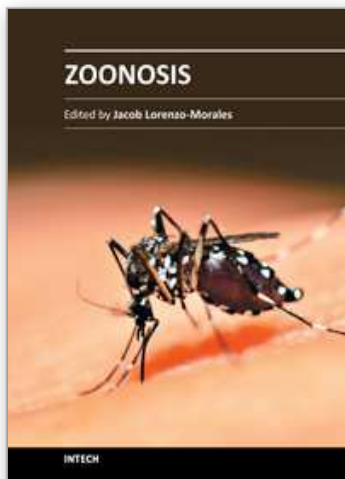
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Zoonosis

Edited by Dr. Jacob Lorenzo-Morales

ISBN 978-953-51-0479-7

Hard cover, 436 pages

Publisher InTech

Published online 04, April, 2012

Published in print edition April, 2012

Zoonotic diseases are mainly caused by bacterial, viral or parasitic agents although "unconventional agents" such as prions could also be involved in causing zoonotic diseases. Many of the zoonotic diseases are a public health concern but also affect the production of food of animal origin thus they could cause problems in international trade of animal-origin goods. A major factor contributing to the emergence of new zoonotic pathogens in human populations is increased contact between humans and animals. This book provides an insight on zoonosis and both authors and the editor hope that the work compiled in it would help to raise awareness and interest in this field. It should also help researchers, clinicians and other readers in their research and clinical usage.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Chandika D. Gamage, Hiko Tamashiro, Makoto Ohnishi and Nobuo Koizumi (2012). Epidemiology, Surveillance and Laboratory Diagnosis of Leptospirosis in the WHO South-East Asia Region, Zoonosis, Dr. Jacob Lorenzo-Morales (Ed.), ISBN: 978-953-51-0479-7, InTech, Available from:
<http://www.intechopen.com/books/zoonosis/epidemiology-surveillance-and-laboratory-diagnosis-of-leptospirosis-in-the-who-south-east-asia-regio>

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