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Leptospirosis a neglected disease of animal and public health importance: An overview

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Abstract
Leptospirosis is a zoonotic infectious disease of bacterial origin caused by spirochete of genus *Leptospira.* It is a disease of global economic importance affecting both humans and animals. Leptospirosis is also known as 7-day fever, harvest fever, field fever, rat catcher's yellows, rice field worker disease, black jaundice. The symptom ranges from none to mild sickness such as headache, muscle pain, fever, acute kidney failure and jaundice, bleeding from the lungs or even meningitis in human beings and causes stillbirths, abortion, repeat breeding, mastitis and reduced milk production in animals. The disease observed almost in all mammalian species and rodents, wild and domestic animals excrete live organisms of *Leptospira* in their urine. Occupations associated with high risk of leptospirosis in humans are slaughter houses, veterinarians and those associated with carrier animals directly and indirectly. The definitive diagnosis can be done by using direct and indirect laboratory methods including isolation of *Leptospira* organisms, Microscopic agglutination Test (MAT) and Enzyme linked immunosorbent assay (ELISA) etc. The treatment includes use of antibiotics like tetracycline, penicillin, ampicillin, doxycycline, streptomycin and erythromycin. The sanitary measures, vaccination, quarantine and rodent control are the most important control measures for prevention of the disease.

Keywords: leptospirosis, microscopic agglutination test, rodents, zoonosis

Introduction
Leptospirosis is neglected but rapidly re-emerging public health problem globally affecting the health of animal and human being. It is most widespread zoonotic disease in the world caused by gram negative pathogenic spirochetes *Leptospira* [6]. The disease is highly dependent on environmental conditions and most commonly prevalent in humid, tropical and sub-tropical climates of South East Asian countries having high rain fall, humidity, presence of marshy land and paddy grown area [11, 38]. Leptospirosis, a contagious disease, is caused by more than 200 leptospiral serovars known to infect almost all mammals [7]. It affects cattle, buffalo, sheep, goat, horse, swine, dog etc. and bacteria are spread through the urine of infected animals or people. Leptospirosis is considered an occupational hazard for many people who work in association with animals directly or indirectly e.g. farmers, veterinarians, abattoir workers, sewer workers etc. The disease is characterized by a broad range of clinical signs which can be observed as septicemia and hemorrhagic syndrome while clinical signs in livestock are usually associated with reproductive losses which result in great economic losses [40]. The direct and indirect laboratory tests used for detection of leptospira are microscopic evaluation, culture, molecular method, serology and animal inoculation [4]. The treatment includes use of antibiotics like tetracycline, penicillin, ampicillin, doxycycline, streptomycin and erythromycin [35] while the prevention of disease can be achieved by sanitary measures, vaccination, quarantine, rodent control and decrease in contact with infected materials, wild animals and rodents [13]. The increased incidence rates and multiple outbreaks of leptospirosis throughout the world [41] resulted in increasing one health problem worldwide. Although leptospirosis is common disease in tropical and subtropical region with significant zoonosis and mortality in both animals and humans but it is not well recognized and neglected due to lack of information and awareness about the extent of the problem. There is also paucity of well documented information about the leptospirosis, Therefore, the objectives of this article were to review impact of leptospirosis on animal health as well as on human beings.

Historical Background
In 1886, the disease was first reported by physician Adolf Weil. Inada and Ito first identified Leptospira as the causative organism in 1908 [14, 15].

It is observed that leptospirosis infected seven to ten million people each year. In India, the disease was first described in Andaman Islands as Andaman haemorrhagic fever in humans [34]. The number of leptospirosis outbreaks has been encountered in Tamil Nadu, West Bengal, Gujarat, Kerala, Orissa, Maharashtra, Karnataka and Andaman and Nicobar Islands [36] and 20th century onwards leptospirosis became endemic in India. The disease is most common in humid climatic conditions, so incidences are more during October-november correlating with monsoon season. In cattle, leptospirosis was first reported in 1960 [1]. Since then several findings confirmed the prevalence of leptospirosis in humans and bovines from different states of India [32, 25, 16].

Epidemiology

Causative agent and its distribution

Leptospirosis is a global zoonosis problem, caused by bacteria *Leptospira interrogans*. *Leptospira* is long corkscrew-shaped organism, too thin to be visible under the microscope. The causative agent is a spirochete measuring 0.1 to 0.2 µm in diameter and having 6-25 µm length with tightly set coils, highly motile by rotating and bending, obligate aerobes. Usually one or both ends of the organism are bent or hooked. Two axial periplasmic flagella are located in the periplasmic space. *Leptospira* organisms are susceptible to heat, dry environment, acids and basics disinfectants but can resist alkali pH up to pH 7.8 [20, 28] and aerobic in nature. The genus *Leptospira* includes two types of species based mainly on their pathogenicity: pathogenic and saprophytic. *Leptospira interrogans* consist of pathogenic strains while *L. biflexa* consist of non-pathogenic free living saprophytic strains. The saprophytic and pathogenic strains of leptospires are not distinguishable on basis of morphology [2]. All pathogenic strains of leptospires were previously classified as members of the species *Leptospira interrogans*, later the genus of *Leptospira* has been reclassified into 20 species including nine pathogenic, six saprophytic species and five intermediate species. Most of pathogenic serovars reported worldwide belongs to three species namely *L. interrogans*, *L. borgpetersenii*, and *L. kirschneri* [26]. Recently the genus *Leptospira* is divided into 35 species belonging to three phylogenetic clusters, which supposedly correlate with the bacterial virulence [39]. In current scenario, there are approximately 300 pathogenic *Leptospira* serovars identified based on their antigenic relatedness; which are indistinguishable based on their morphology. Usually, every serovar is adapted to a specific mammalian host like insectivores, rodents, pigs, dogs and cattle. Each serovars can be observed into several hosts, while one host may have more than one serovars except Hardjo infection where the serovar Hardjo is specifically observed in cattle and sheep only and there are no known wildlife hosts to this serovar [12]. Rodents, domestic & wild animals are the reservoir of infectious organisms. The domestic animals such as cattle, dogs, and pigs may act as carriers for several months while rodents usually remain carrier throughout their life (permanent carrier). Rodents are therefore supposed as the major reservoir of infection. Leptospires are excreted in the urine of the infected/carrier animals and they affect man when he comes into contact with urine of infected animals, directly or indirectly [30]. Leptospirosis can occur in man in both urban and rural areas. In India, urban leptospirosis has been reported from Chennai and Mumbai while rural leptospirosis has been reported from Gujarat, Kerala and Andamans. In other states, the non-reporting of leptospirosis did not mean that it is absent in those states of India [30].

Mode of Transmission

Leptospirosis is mostly transmitted by the urine of an infected animal and bacteria can't survive dryness for a longer period so remain contagious in urine [6]. Although *Leptospira* have been identified in reptiles and birds but only mammals are reported to transmit the bacteria to humans and other animals. Rodents, cattle, pigs, dogs, cats and wild animals are considered as common reservoirs of leptospires. The organism cannot be eradicated since rodents are major natural reservoirs. McKay, 2001 found that pet dogs mostly got infection of *Leptospira*, though licking of urine of infected rodents in the house or outside [22]. The moist and damp habitats like riverbanks, muddy livestock rearing areas where there is a regular passage of wild or farm mammals are mostly carry the infective bacteria [18]. The disease is seasonal in temperate climates and year-round in tropical climates and directly associated with increased rainfall [41]. Leptospirosis can also be transmitted through the semen of the infected animals [41]. Humans can only become infected through contact with food, water, or soil that is contaminated with urine from these infected animals however no human to human transmission of leptospirosis is reported [41]. It is an occupational disease affecting farmers sewer workers, slaughterhouse workers, veterinarians, fish workers and rodent catchers. Individuals working directly with animals like veterinarians, farmers, cowherds, abattoir workers, etc. can acquire the infection through contact with infected urine, infected carcasses, aborted fetuses or parts of placenta and during milking, and after animal bites. The disease is also a recreational hazard has also been associated with swimming, and rafting in contaminated lakes and rivers for campers or those who participate in such activities in tropical or temperate climates.

Pathogenesis

The bacteria enter into the body through intact mucosa (mouth, nose, eyes and vagina) and small abrasions or cuts in skin [2, 33]. It involves some chemotactic interactions and then transmembrane passage through lymphatic system into blood mainstream [10] and then spread to kidneys, liver, spleen, eyes, central nervous system and reproductive organs [19]. *Leptospires* settle down in the renal convoluted tubules and thus chronically shed the causative organisms in urine from a few weeks to many months. Once the bacteria reach to a higher number in blood and tissue, the endotoxins released by the *Leptospires* caused severe tissue damage. Hemolysin is another toxin which is also secreted by the *Leptospires* and leads to lysis of blood cells. The endothelium lining of tissues get damaged due to toxins which leads to ischemia and other complications. The exact molecular basis of virulence of *Leptospires* is yet unknown however the humoral (antibodies) response has been found to be active in first week of infection leading to phagocytosis by macrophages and neutrophils. If the animal or human have high or sufficient antibody titre then body will clear the infected organisms and no clinical signs will appear. If the antibody titre is not sufficient then disease will develop manifested by the appearance of clinical signs. The incubation period is varied between 7-14 days depending upon the infectious strain, dose of organisms and host affected.

Clinical Signs and Symptoms

Leptospirosis is characterized by a wide range of clinical symptoms in livestock with slight difference between affected species. Clinical signs of acute or sub-acute disease are seen in the leptospiremic phase and it is characterized by septicaemia, anorexia and high fever, depression, petechiation of mucosa, paleness, and acute hemolytic anaemia with hemoglobinuria and jaundice. Clinical signs of chronic leptospirosis in livestock are generally associated with reproductive problems like infertility, stillbirth, abortion, drop in milk production and mastitis. Abortion in animals usually occurs during the last trimester of pregnancy [3]. Bovine leptosirosis is one of the major causes of reproductive failure. The clinical signs linked with bovine leptospirosis are variable and depend upon the infecting serovar as well as the susceptibility of the individual animals [2]. Serovars viz., Hardjo, Pomona, Icterohaemorrhagiae, Australis, Hebdomadis, Bankinang and Grippotyphosa are found mainly associated to bovine leptospirosis. *Leptospira* infection occurs via bacterial exposure through mucous membranes and results in no or very mild acute clinical symptoms. As a result of serovar Hardjo infection, abortions, birth of weak calves or stillbirths may occur, but the symptoms are usually seen only when animal is infected during her first pregnancy. Abortion may occur several weeks after the infection without any noticeable signs of illness. Infertility is also commonly seen in bovine leptospirosis. Persistent infection of the reproductive tract of the male and female cattle may be the most economically important feature of serovar Hardjo infection. The disease has enormous economic impact on the international trade of animals and semen also [5]. Small ruminants are considered as accidental hosts, being affected by incidental serovars of *Leptospira*, carried by other domestic and wild animals. The disease occurs rarely in sheep and goats but the symptoms are similar to the bovines with major illness only in young or pregnant animals. In most cases they develop acute septicemia and are found dead. In Hardjo infections, abortion may be the only sign, but milk drop syndrome can also be observed.

Canine leptospirosis is characterized by anorexia, lethargy and vomiting, weight loss, polyuria, diarrhea, abdominal or lumbar pain, musculoskeletal pain and dehydration. The clinical symptoms of equine leptospirosis are similar to those of cattle, with listlessness, low-grade fever, anorexia, anaemia, conjunctival suffusion, petechial hemorrhages on the mucosa, jaundice, and general depression. Renal failure may also occur, especially in foals. In pregnant mares infection may results in abortion, placentitis and stillbirths [31].

In humans, the clinical manifestations of leptospirosis are flu-like illness, pneumonia, pulmonary hemorrhages, jaundice, acute kidney failure, etc [17]. The disease is characterized by fever, myalgias, severe headache, chills, nausea and vomiting, diarrhoea, anuria or oliguria, jaundice (yellowing of skin and eyes), conjunctival suffusion, haemorrhages, aseptic meningitis, skin rash, joint pain, cardiac arrhythmia, psychosis and restlessness. Many of these symptoms can be mistaken for other diseases. In addition, some infected persons may have no symptoms at all. Sometime infected persons may not have any symptoms. Illness usually starts suddenly with fever and other symptoms appear after 7-12 days incubation period. The classical form of severe leptospirosis is known as Weil's disease which is characterized by jaundice, bleeding and kidney failure [12]. The disease affects brain also causing meningitis, encephalitis of brain tissue with same signs and symptoms; and lung affected as the most serious and life-threatening of all leptospirosis complications.

Leptospirosis may occur in two phases-

- The first phase (acute or septic phase) ends after 3–7 days of illness with the appearance of antibodies against Leptospira and the disappearance of all the bacteria from the bloodstream. The patient is asymptomatic for 3–4 days until the second phase begins with another episode of fever.
- The hallmark of the second phase is meningitis (inflammation of the membranes covering the brain) the illness lasts from a few days to 3 weeks or longer. Without treatment, recovery may take several months

Majority of the cases of the leptospirosis are mild form. However, there has been reports of severe disease, which develops during the second stage or occurs as a single progressive illness.

Diagnosis

Proper diagnosis of leptospirosis is mainly based on laboratory confirmation since its clinical signs are nonspecific and can be usually mistaken with other febrile diseases. The clinical signs should be correlated with the medical history like low-lying areas, seasonality, contact with stagnant contaminated water or rodents in vicinity to support the leptospirosis hypothesis which will serve as indication for specific tests.

After infection with the bacteria, *Leptospira* can be observed in blood and cerebrospinal fluid (CSF) during first 7 to 10 days and then moving to the kidneys. After a period of 7 to 10 days of infection the microorganism can be observed in fresh urine. Hence, early diagnostic efforts include isolation of bacteria from blood or other clinical materials through culture of pathogenic *Leptospires. The organism of Leptospira* can be cultured in (Ellinghausen-McCullough-Johnson-Harris) EMJH medium, which is need to be incubated at 28° to 30 °C for a period of more than month. Since, *Leptospires* growth required a period of incubation more than a month, so its isolation is difficult. In laboratory, diagnosis of leptospirosis is broadly classified into direct diagnosis or confirmation by isolation of causative organism or demonstration of leptospires by dark field microscopy or by PCR amplification of specific segment of leptospiral genome; and indirect diagnosis by detection of antibodies against leptospires using Microscopic agglutination Test (MAT), Enzyme linked immunosorbent assay (ELISA), Lepto dipstick assay and Indirect haemagglutination assay (IHA).

Among serological tests, MAT is the most widely used reference and gold standard serological test for diagnosis of leptospirosis [24]. This test needs live bacterial antigen to test so it is a very laborious and expensive method and that's why this test is only conducted in specially designed labs [27]. For MAT test live organisms of *Leptospira* are needed to be cultured on regular basis and agglutination reaction is carried out to check the species and serovar of the *Leptospira.*

Diagnosis of *Leptospira* antibodies by ELISA is serovar-specific serovar-specific and thus limited to regions where the occurrence of the serovars is well defined. ELISA technique can detect specific immunoglobulin IgM and IgG [8] in response to bacteria so can distinguish acute and chronic infections. For the rapid, easy and visual detection of *Leptospira*, label-based lateral flow dipstick assay was

developed using multiplex loop-mediated isothermal amplification (m-LAMP) which can simultaneously detect the target DNA template and a LAMP control in clinical diagnostics thus serving as a point-of-care device [23]. For diagnosis lipL32 gene which is highly conserved among pathogenic *Leptospira* serovars, an electrochemical AuNPs based highly sensitive and specific DNA sensor has been developed [37].

Treatment

In cases where symptoms are suggestive of leptospirosis, it is utmost important to contact a doctor as soon as possible for its confirmation. The antibiotics like tetracycline, penicillin, ampicillin, doxycycline, streptomycin and erythromycin are advised for treatment of disease [35]. Most of time, animals are presented for the treatment only when the septicaemia has subsided, so results are disaapointed. The secondry aim of treatment is to control the secretion of *Leptospires* in the urine so that infected animal did not act as carrier for other, which can very well achieved by the use of above mentioned antibiotics. Fluid therapy, blood transfusion and other symptomatic care can also be advised depending upon the condition of the infected animal or human being.

Prevention and Control

Due to the wide prevalance of leptospires in wildlife and reservoir hosts, the prevention and control of leptospirosis is difficult in domestic animals as well as in human being. The carrier animals who are shedding the *Leptospira* organisms in their urine should be segregated or slaughtered. The infected animals should be immediately isolated and quarantined for at least 14 days. The premises and surroundings of infected animals should be thoroughly disinfected. The risk of leptospirosis can be reduced by avoiding water contaminated with animal urine or contact with potentially infected animals. Since, leptospirosis is disease of an occupational hazard, all the persons directly involved with animals and its surrounding should preferably use aprons, gloves, gumboots and other protective equipment during their handling. Any skin cuts should be covered with waterproof dressing while swimming in freshwater to protect against a range of infections. Destruction of mice and rodents using effective rodenticides, is a necessary step towards prevention of leptospirosis [9]. Since rats and other wild animals act as infection source, contact between them and farm animals should be controlled by using rat bait and fencing of farm [21]. Control of leptospirosis includes measures like identification and treatment of the carriers and infectious source and systematic immunization with commercially available vaccines containing the circulating serovars. Immunization of local reservoirs of the pathogen should be implemented in the areas which are highly prone to leptospirosis especially low lying areas, damp and muddy environment and high rice cultivating areas [29]. Environmental modifications such as draining wet areas may decrease the incidence of disease, but are not always feasible or desirable. Although vaccination is not possible in wild animals, but the vaccination strategy can be applied in domestic animals for control and prevention of leptospirosis. Currently the molecular and cellular studies on leptospirosis vaccines have been focused on whole cell inactivated immunogen, lipopolysaccharides, lipoproteins, outer-membrane proteins and potential virulence factors [38].

Conclusion

Leptospirosis is an important neglected zoonotic disease of endemic nature in India with considerable impact on veterinary and public health. The main causes of spread of disease are urine of infected or carrier animals and environment contaminated with infected organisms. The other determinants which play role in spread of leptospirosis are climatic condition, environmental hygiene and association of humans in certain specific occupations. Leptospirosis can be easily treated with antibiotics after confirmation with laboratory methods. Strict bio-security measures like quarantine and isolation of infected or suspected animals should be implemented for the successful control and eradication of the leptospirosis. Leptospirosis in human beings can also be controlled by reducing its prevalence in domestic and wild animals. Based on concept of one health, an interdisciplinary approach involving medical, veterinary, agricultural and environmental sciences needs to be implemented in order to prevent and eradicate the leptospirosis.

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