A global one health perspective on leptospirosis in humans and animals

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ABSTRACT
Leptospirosis is a quintessential one health disease of humans and animals caused by pathogenic spirochetes of the genus Leptospira. Intra- and interspecies transmission is dependent on 1) reservoir host animals in which organisms replicate and are shed in urine over long periods of time, 2) the persistence of spirochetes in the environment, and 3) subsequent human-animal-environmental interactions. The combination of increased flooding events due to climate change, changes in human-animal-environmental interactions as a result of the pandemic that favor a rise in the incidence of leptospirosis, and under-recognition of leptospirosis because of nonspecific clinical signs and severe signs that resemble COVID-19 represents a “perfect storm” for resurgence of leptospirosis in people and domestic animals. Although often considered a disease that occurs in warm, humid climates with high annual rainfall, pathogenic Leptospira spp have recently been associated with disease in animals and humans that reside in semiarid regions like the southwestern US and have impacted humans that have a wide spectrum of socioeconomic backgrounds. Therefore, it is critical that physicians, veterinarians, and public health experts maintain a high index of suspicion for the disease regardless of geographic and socioeconomic circumstances and work together to understand outbreaks and implement appropriate control measures. Over the last decade, major strides have been made in our understanding of the disease because of improvements in diagnostic tests, molecular epidemiologic tools, educational efforts on preventive measures, and vaccines. These novel approaches are highlighted in the companion Currents in One Health by Sykes et al, AJVR, September 2022.

Leptospirosis is a globally important, zoonotic bacterial infection of humans and animals caused by Leptospira spp that incorporates all facets of a one health problem. Effective prevention requires a transdisciplinary approach in order to understand the way pathogenic spirochetes interact with incidental hosts, the environment, and vertebrate reservoir hosts. Over 300 pathogenic serovars have been identified, classified based on their outer lipopolysaccharide antigens. Serovars are organized into antigenically related serogroups. Leptospira strains are also classified based on DNA sequence composition (sequence types). Based on sequence information, the 64 known species of Leptospira are grouped into 2 pathogenic subsclades (P1 [Pathogens 1, pathogenic species] and P2 [Pathogens 2, intermittently pathogenic]) and 2 saprophytic subsclades (S1 and S2). Saprophytic organisms live in the environment and are poorly associated with mammalian host species. The P1 subsclade is further divided into high-virulence and low-virulence pathogenic species. Most leptospirosis in humans and animals results from infections by P1-virulent species such as Leptospira interrogans, Leptospira kirschneri, Leptospira borgpetersenii, and Leptospira noguchii, although P2 species have been recognized as a cause of severe disease in some cases. Infections follow exposure of mucous membranes or abraded skin to pathogenic strains that are shed from the renal tubules of infected reservoir hosts. These organisms contaminate soil and water and can remain viable in the environment for weeks to months when conditions are optimal. Biofilm formation may contribute to the ability of the spirochete to persist in the environment and in renal tubules of reservoir hosts.

Leptospirosis in Humans
Most human infections with pathogenic leptospires are self-limited and/or subclinical. When disease occurs, it ranges from a mild, febrile, flu-like illness to a severe multisystemic disease that is as-
associated with acute renal failure, hepatic injury, and sometimes pulmonary hemorrhage, meningitis, and pancreatitis after an average incubation period of 7 to 12 days (range, 3 to 30 days). Transplacental infections can occur during pregnancy with abortion or stillbirth. The estimated global burden of disease in humans is 1.03 million cases annually, with 58,900 deaths. In 1 systematic survey, morbidity and mortality were highest in the Institute for Health Metrics and Evaluation Global Burden of Disease regions of South and Southeast Asia; Oceania; the Caribbean; Andean, Central, and Tropical Latin America; and Eastern Sub-Saharan Africa. Because leptospirosis in humans is often a nonspecific illness and available diagnostic tests lack sensitivity, the vast majority of cases are likely either not recognized or not reported. Human leptospirosis also resembles COVID-19, and mixed infections with SARS-CoV-2 and Leptospira have been described. With the current focus on COVID-19, the overlapping clinical picture is likely to contribute to misdiagnosis of leptospirosis cases as COVID-19, with insufficient attention to prevention strategies.

The country with the highest incidence of leptospirosis worldwide is Sri Lanka, with over 700 deaths per annum (more than twice that for dengue fever) and an estimated annual incidence for hospital admission of 52.1 patients/100,000 population. (These numbers must be interpreted with caution, as they are based on broad surveillance case definitions, including clinical suspicion in the absence of confirmation using complete diagnostic testing and exclusion of other causes.) Rice paddy work is an important risk factor in Sri Lanka as well as in Thailand, India, Indonesia, Iran, the Philippines, Tanzania, and Korea; the disease has thus been termed rice field fever. In developed countries, disease is most often recognized in people with occupational activities that involve water exposure or interactions with animal reservoir hosts or in people participating in recreational activities involving water. Wildlife trapping for research purposes, production animal work (abattoir work, dairy farming, veterinarians working with livestock), water-intensive crop farming (bananas, pineapples, taro, rice, berries), military operations, fish farming, and sewer work increase risk for leptospirosis. Recreational activities associated with increased risk of disease include adventure racing, canoeing, kayaking, caving, open-water swimming, triathlons, and white-water rafting. Increased popularity of these activities over the last 20 years has been followed by reports of often significant outbreaks of disease. Inadequate housing infrastructure and sanitation in resource-poor communities increase risk because of exposure to infected rodents and potentially also free-roaming dog populations. Although this primarily has been a problem in resource-poor countries, reports of leptospirosis in urban regions of southern Europe, the US, and the UK in recent years suggest that leptospirosis could emerge due to increased homelessness following natural disasters and major financial crises, such as that related to the COVID-19 pandemic.

Leptospirosis in Animals

In addition to widespread subclinical infection in an enormous variety of animal reservoir hosts, pathogenic leptospires cause disease in dogs, cattle, horses, pigs, camelds, small ruminants, and wildlife species. The clinical picture of leptospirosis in dogs resembles that in humans, in that most infections are subclinical, but when disease occurs, it is typically characterized by signs of lethargy, fever, inappetence, and polyuria/polydipsia, then multigorgan dysfunction with acute kidney injury, cholestatic hepatic dysfunction, pancreatitis, variable degrees of pulmonary hemorrhage, myositis, and, in some cases, uveitis. In cattle, the spirochete is a major cause of abortion, neonatal illness, and production loss such as decreased milk production worldwide. Most disease in cattle worldwide has been attributed to L. borgpeterseni serovar Hardjo (Hardjobovis); others include L. interrogans serovar Hardjo (Hardjobovis), and L. interrogans serovar Pomona, as well as a large number of other serovars that belong to other serogroups. However, challenges associated with diagnostic testing have limited a full understanding of the most important serovars causing disease, and prevalent serovars vary geographically. When severe acute multisystemic disease occurs, it usually occurs in calves in association with signs of fever, hemolytic anemia, hemoglobinuria, and icterus. Blood-tinged milk and agalactia can occur in lactating cows. Risk factors identified for Hardjo infection in cattle are open herds, access to contaminated water sources, cograzing with sheep, use of natural service (rather than artificial insemination), and herd size. Subclinical infection of cattle in a herd can serve to perpetuate disease within the herd. Shedding can continue intermittently for months in the absence of detectable serum antibodies.

Production losses, reproductive failure with abortions, stillbirths, and neonatal illness also occur in pigs and small ruminants. Leptospirosis is well recognized globally as a major cause of reproductive failure in pigs, with serogroups Tarassovi, Pomona, and Australis predominating. Incidental infections in pigs may be associated with hemorrhagic disease, hematuria, icterus, and acute kidney injury. Movement to indoor housing appears to have reduced the incidence of disease.

Disease in horses may be associated with febrile illness, reproductive losses, and neonatal illness. In North America, L. interrogans serovar Pomona (type Kennewickii) is thought to be the main pathogenic species involved, followed by L. kirschneri serovar Grippotyphosa; again, serovars and strains likely vary geographically. A single genotype of L. interrogans serovar Pomona (Kennewickii) was associated with the majority of abortions in horses in Kentucky, based on culture and typing efforts. Foals may develop acute kidney injury, and recurrent uveitis can follow infection in adult horses. In North America, leptospirosis has been estimated to account for 50% of recurrent uveitis cases in horses, and this is considered the most economically significant impact of leptospirosis in horses. As in hu-
Humans, uveitis occurs weeks to years after initial infection; however, in contrast to humans, the disease is progressive rather than self-limiting. In the absence of aggressive therapy (vitrectomy), it frequently leads to unilateral or bilateral blindness. For years, this condition was thought to be a postinfectious syndrome with an immune-mediated basis. This was based on an apparent lack of detectable spirochetes in the eye, evidence of molecular mimicry in some studies, poor response to antimicrobial therapy, and response to glucocorticoid treatment. However, a 2021 study from Germany that examined equine eyes after vitrectomy indicated that biofilm formation within the eye may explain resistance to systemic antimicrobial therapy.

Isolated cases and outbreaks of leptospirosis have been uncommonly described in captive and free-ranging wildlife species. Reports of leptospirosis in captive wildlife species have included a tiger (Panthera tigris sumatrae), southern tamanduas (Tamandua tetradactyla), and nonhuman primates. Affected free-ranging wildlife species have included nonhuman primates, canids and felids, Eurasian beavers (Castor fiber), and marine mammals on the west coast of the US. Affected marine mammals have included northern sea otters (Enhydra lutris kenyoni), northern elephant seals (Mirounga angustirostris), harbor seals (Phoca vitulina richardsi), and California sea lions (Zalophus californianus).

### Roles of Pathogen, Host, and the Environment

Pathogen factors, reservoir host animals, and environmental factors play critical roles in the maintenance of transmission. After burrowing through tissues at the site of inoculation, spirochetes rapidly multiply in the bloodstream. Organism virulence factors and an individual host’s immune response to the pathogen impact outcome of infection. When virulent strains attain a high burden of infection in the blood, a cytokine “storm” ensues, with fever and multiorgan failure. Possession of the human leukocyte antigen DQ6 was an independent risk factor for severe outcome in 1 outbreak among triathletes contributing to the development of immune activation. In other hosts, organism replication is controlled and ultimately limited to the proximal tubular lumen of the kidney; organisms attach to the brush border on tubular epithelial cells and are shed in urine for weeks to months, with evasion of host immune responses. The organism forms biofilms within the renal tubules that may contribute to its persistence in the face of the immune response and antimicrobial therapy. Although a distinction has been made between incidental hosts and reservoir hosts, the recognition of reservoir host-associated leptospiral strains in disease outbreaks affecting those reservoir hosts suggest that a continuum of infection outcomes may exist and that host factors such as immunosuppression may be important in influencing such outcomes. For example, in California sea lions, cyclical outbreaks of disease in yearlings are accompanied by continuous subclinical infections in the adult sea lion population, with shedding documented for up to 154 days after infection. We recently isolated L. interrogans serovar Canicola from dogs in association with an outbreak of leptospirosis in pet dogs in Los Angeles (J. E. Sykes, J. Sebastian, K. L. Reagan, et al, unpublished data, 2022); dogs have typically been considered reservoir hosts for serovar Canicola, so again other factors, such as pathogen strain variation or host immunosuppression (associated with overcrowding in boarding kennels), may be impacting disease expression.

The duration of urinary shedding depends somewhat on the degree of adaptation between the leptospiral strain and the specific reservoir host involved. A large variety of warm-blooded or poikilothermic domestic animal and wildlife species can act as subclinical carriers. Globally, rodents (especially Rattus norvegicus) are considered to be the most important reservoir hosts because of the high prevalence of infection in some rodent populations (up to 90%) and the high concentration of spirochetes in the urine of rodents when compared with other animal species. Exposure to rodents is a well-established risk factor for infections in humans and domestic animals under a variety of circumstances. Humans and animals become infected by pathogenic leptospires when intact mucous membranes, macerated skin, or abraded skin is exposed to contaminated environmental sources (such as water or mud). Animals can also become infected following direct exposure to infected urine or tissues of reservoir hosts. Therefore, in addition to exposure to contaminated water sources, predation of species such as rodents and lizards by dogs should be considered as a potential mode of transmission. Pathogenic leptospires have been found in the reproductive tracts of domestic cattle, pigs, sheep, and wild boar, so venereal transmission may be possible and could maintain transmission when environmental conditions do not favor survival of the spirochete outside the mammalian host. Leptospira borgpetersenii serovar Hardjo has also been detected in fresh raw milk, suggesting that infection may also be transmitted through consumption of unpasteurized milk products.

Although it was thought that pathogenic leptospires could only replicate in infected hosts and not in the environment, a 2022 study found that the organism could replicate in waterlogged soil, but not in soil or water alone. This could ultimately explain why outbreaks of leptospirosis follow flooding after a lag time, typically 1 to 3 months. In a meta-analysis that documented an association between flooding incidents and leptospirosis, once flooding had occurred, being male, the existence of lacerated wounds, and exposure to livestock animals increased risk for leptospirosis; “sighting of rats” slightly increased the risk. Climate change has been associated with increased flooding events across the globe, and there has been widespread concern that this ef-
fect, combined with growth of the human population and urbanization, will dramatically increase the risk of leptospirosis.\textsuperscript{1,69,70}

Continuing Emergence of Leptospirosis During the COVID-19 Pandemic

Amid climate change concerns, the COVID-19 pandemic has resulted in unprecedented disruption to human lives that may have increased the risk of leptospirosis. According to the World Health Organization, tens of millions of people are at risk of extreme poverty, and nearly half of the world’s 3.3 billion global workforce are at risk of losing their livelihoods.\textsuperscript{71}

The World Health Organization emphasizes the profound negative impact of the pandemic on the livelihood of agricultural workers, a group that were already at increased risk for leptospirosis, especially in developing countries where climate conditions are optimal for survival of leptospires in the environment. The incidence of some infectious diseases has decreased due to improved hygiene and aggressive lockdowns. A large study\textsuperscript{72} from Zhejiang province on the east coast of China (China’s second-richest province, with a population of 64.6 million people) examined the effect of pandemic restrictions on the incidence of 19 common infectious diseases (1.8 million incident cases between January 2017 and October 2020). The incidence of infectious disease overall dropped by 71%, with the largest decrease noted for influenza. However, the incidence of 2 diseases, leptospirosis and severe fever with thrombocytopenia syndrome (caused by the tick-borne virus 	extit{Dabie bandavirus}), increased. Sri Lanka has been recognized for its aggressive approach to containment of COVID-19.\textsuperscript{73,74}

In 2020, the number of leptospirosis cases reported to Sri Lanka’s surveillance system was the highest ever—8,579 cases and more than 800 estimated deaths.\textsuperscript{75} This compared with 7,423 cases in 2008, the last time a large increase in leptospirosis occurred. Monthly case numbers increased dramatically in May 2020, shortly after imposition of aggressive lockdowns, and were maintained at levels above those for January through April for the remainder of the year.\textsuperscript{75} There were 3,404 cases during the second quarter of 2020, an increase of 38.5% compared with the same period in 2019. In contrast, the number of Dengue fever cases declined from the previous year by 73.6%, possibly because of a drier first quarter of 2020, closure of schools and offices, and aggressive street and home cleaning that may have reduced mosquito breeding sites.\textsuperscript{76} It was suggested that the surge in leptospirosis may have occurred because of increased paddy field activity following the lockdowns as well as nonimplementation of a state-sponsored doxycycline prophylaxis program for individuals at risk during the pandemic.\textsuperscript{75,76} Lockdowns were thought to have created the greatest economic impact on farmers engaged in cropping of perishables, such as vegetables; in contrast, rice was less prone to problems associated with market interruptions.\textsuperscript{77}

With a drier first quarter of 2020 than usual and no unusual increases in rainfall for the remainder of 2020, rainfall patterns could not explain the increase in leptospirosis cases. Examination of changes in livestock numbers in regions with the highest cumulative incidence of leptospirosis in 2020 revealed a decrease in cattle and water buffalo populations from 2019 to 2020. The number of poultry and swine farms also decreased in the most impacted regions; although poultry are not reservoir hosts for 	extit{Leptospira}, poultry farming can encourage rodent activity.\textsuperscript{78,79}

In the US, human homelessness was rising before the onset of the pandemic. The Annual Homeless Assessment Report to Congress, which provides point-in-time estimates of the number of sheltered and unsheltered homeless people during the last 10 days of January of each year,\textsuperscript{80} estimated that in January 2020, the number of unsheltered homeless had increased by 7% compared with the number in January 2019; the number of sheltered homeless was unchanged.\textsuperscript{80} Although there have been visible rises in the unsheltered homeless and homeless encampments in major cities across the US, the impact of the pandemic on the size of the unsheltered homeless population in 2021 has not yet been quantified.\textsuperscript{81} The 2021 Annual Homeless Assessment Report reported data only for the sheltered homeless, as communities chose not to conduct point-in-time counts of unsheltered homeless because of limited capacity and concerns about transmission of SARS-CoV-2.\textsuperscript{82} The number of people in sheltered locations decreased by 8% between 2020 and 2021, possibly because of government aid and efforts to decrease crowding of shelters in response to the pandemic. While there was no increase in the communities that did conduct unsheltered counts, this count represented only 22% of unsheltered homelessness in 2020\textsuperscript{82}; almost the entire state of California was said not to have reported counts.\textsuperscript{81} Although not yet published in the peer-reviewed literature, there were reports of several likely cases of leptospirosis in homeless people on the East Coast in the popular news media in the US during October 2021. Although there is a paucity of recent studies, it has been estimated that as many as 25% of homeless people own pets, with the majority of those owning dogs.\textsuperscript{83,84} The growth of homeless encampments in association with the pandemic; the close proximity between rodents, dogs, and humans in these encampments; increased environmental contamination by pathogenic leptospires in association with climate change–associated flooding events; and the similar clinical manifestations between COVID-19 and leptospirosis present a “perfect storm” for unrecognized outbreaks of leptospirosis in developed countries such as the United States.

Prevention Strategies

A variety of strategies are available for prevention of leptospirosis. Whole bacterin vaccines are available for dogs, cattle, pigs, and, in the US, horses. Annual vaccination of cattle has also been shown to

\textsuperscript{1,69,70,72,73,74,75,76,77,78,79,80,81,82,83,84}

\textsuperscript{1,69,70,72,73,74,75,76,77,78,79,80,81,82,83,84}
reduce leptospiruria with an efficacy of 89.9%, and in New Zealand, a reduction in the annual incidence of reported leptospirosis appeared to coincide with implementation of dairy cattle vaccination in the late 1970s, from an annual incidence of 15.7/100,000 in 1970 to 1979 to 4.4/100,000 in 1990 to 1998. However, even in countries where disease is widely recognized in cattle, vaccination is not widely performed; in Sri Lanka, vaccination of cattle is not performed at all. Bivalent vaccines that contain *L. interrogans* serovars Icterohaemorrhagiae and Canicola have been available for prevention of leptospirosis in dogs since the 1970s and are still used in many countries. In the US and Europe, the continued appearance of disease in dogs vaccinated with serovars Canicola and Icterohaemorrhagiae prompted inclusion of 2 additional serovars based on regional seroreactivity data (Pomona and Grippotyphosa in the US since 2001; Grippotyphosa and Australis or Bratislava in other countries). Since introduction of 4-serovar vaccines, virtually all dogs with leptospirosis seen at the teaching hospital of one of the authors (JES) have been dogs without a history of vaccination with 4-serovar vaccines. Vaccines also have been used to protect humans in response to outbreaks in some countries (such as China, Japan, Korea, and France). In Korea, implementation of vaccination programs was followed by a dramatic reduction in the incidence of leptospirosis in paddy field workers. Vaccines provide immunity that is serogroup specific at best, and efforts continue to develop broadly protective, cost-effective human leptospirosis vaccines with a low adverse-effect profile and robust duration of immunity. Because of the serovar-specific nature of current vaccines, vaccination programs are likely to be most effective when there is an understanding of *Leptospira* species and serovars circulating in the domestic animal species targeted for vaccination. When the goal of vaccination of a particular animal host is to prevent disease in exposed humans as well as to prevent disease in the vaccinated host, the design of serovar-specific vaccines must depend on a knowledge of 1) regionally important serovars shed by that animal that are capable of causing disease in humans but which might not cause disease in the animal host species (often the case for reservoir hosts) and 2) regionally important serovars likely to cause disease in that animal (eg, acute kidney injury in dogs).

Targeted education of those at risk of leptospirosis regarding preventive measures may reduce the incidence of disease. In agricultural regions in developing countries, such measures include wearing protective clothing, exclusion of production animals from the home, removal of fecal contamination, handwashing before eating and after interacting with animals, boiling environmental water before drinking, avoidance of bathing in open-water sources and walking through mud with bare feet, proper bathing after walking in paddy fields, rodent control, and prompt seeking of proper medical care following onset of febrile illness. Understanding the baseline level of knowledge and attitudes among at-risk humans is important to guide educational efforts. A 2020 study of paddy cultivators in Sri Lanka regarding perceptions and knowledge about leptospirosis found that although there was a high degree of awareness about the disease and appropriate preventative measures, only about 20% of respondents claimed to wear boots and gloves because wearing them was felt to be cumbersome. Many respondents reported taking traditional medicines first for fever rather than appropriate anti-leptospiral antibiotics.

Prophylactic doxycycline treatment was protective in a study of “Eco-Challenge” athletes in Malaysian Borneo. The use of doxycycline to prevent leptospirosis in paddy field workers in India and military personnel in Panama was associated with a reduction in disease incidence. Weekly (200-mg) doxycycline treatment has been used in Sri Lanka to prevent leptospirosis in paddy workers during harvesting seasons. However, despite widespread awareness of the availability of chemoprophylaxis, compliance has been low because of perceived immunity, lack of motivation, lack of availability, or concerns regarding adverse effects. Increased efforts to deliver doxycycline to at-risk workers or development of sustained-release formulations of doxycycline that improve compliance should be considered to improve the efficacy of chemoprophylaxis efforts. However, such approaches have the potential to increase risk for selection of other antimicrobial-resistant bacteria; to date, there have been no reports of acquired antimicrobial resistance within *Leptospira* spp.

Conclusions

In conclusion, leptospirosis represents a classic one health problem that requires a thorough knowledge of mechanisms of transmission, animal reservoir hosts involved, environmental sources of the organism and climatic factors that influence transmission, and the impact of human occupational and recreational behavior patterns. These factors vary regionally and over time, requiring ongoing global surveillance efforts. Improvements in treatment and prevention of this disease will require advancements in diagnostic test turnaround time, sensitivity, and specificity; application of novel genomic approaches to better understand the epidemiology of the disease; ongoing education of at-risk people and animal owners globally; and the development of novel, low-cost vaccines that provide protection against a broad range of strains with minimal adverse effects. Advances in technology that will continue to play a key role in these efforts are discussed in the companion Currents in One Health by Sykes et al, *AJVR*, September 2022.

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