Epidemiology of Leptospirosis

Subjects: Veterinary Sciences

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Leptospirosis is a zoonosis that is prevalent worldwide and has major impacts on both humans and animals. The disease is caused by species of *Leptospira,* a spirochaete bacterium with increasing genetic diversity.

Leptospira | one health | diagnosis | epidemiology

1. Introduction

Leptospirosis is a zoonosis that is prevalent worldwide and has major impacts on both humans and animals [1][2]. The disease is caused by species of *Leptospira*, a spirochaete bacterium with increasing genetic diversity [3][4]. To date, 38 species of pathogenic *Leptospira* have been described, and new species are continually being discovered [5]. The morbidity and mortality rates of leptospirosis in humans are estimated at 1 million and 60,000 cases, respectively [6]. Of the reported cases, 2.90 million disability-adjusted life years are estimated to be lost per annum [7]. Various human-acquired syndromes, ranging from flu-like to life-threatening hepatorenal syndromes, have been described to be associated with leptospirosis in the literature [8][9][10]. In severe cases, mortality rates vary between 5% and 20% [6]. Humans, as well as wild and domestic animals, can be infected either directly following contact with the body fluid of *Leptospira*-infected animals or indirectly when exposed to environments contaminated by leptospirosis [11][12][13][14]. Animal *Leptospira* infection presents not only as acute clinical manifestations observed in humans but also as a chronic infection that can lead to major economic depletion due to reproductive failure [2]. Following several human leptospirosis outbreaks reported worldwide [15], this infectious disease has been categorized as a (re-) emerging disease and is still qualified as such by the World Health Organization (WHO) [16].

The limit of understanding of the natural history of *Leptospira* infection and the under-recognition of its burden are due to insufficient diagnosis, largely as a result of the two stages experienced by the host [17][18]. The first stage of leptospirosis is the septicemic or acute stage, which occurs in the first week of infection, wherein the host generally shows symptoms of *Leptospira* circulating in the bloodstream [1][2][17][19]. The second stage of the disease is the immune stage, which generally occurs in the second week of infection, wherein the host starts to acquire and show anti-*Leptospira* antibodies in the serum [1][2][17][19]. Currently, the most accurate test to detect the acute phase of infection is the polymerase chain reaction (PCR) [18]; this technique is highly sensitive and can rapidly detect the *Leptospira* species [17][20]. Treatment following a positive PCR result at this stage might be effective, unlike the culture and microscopic agglutination test (MAT), which is less advantageous for early diagnosis. Culture is time-consuming and known for its difficulty in isolating *Leptospira*, whereas the MAT only detects antibodies indicating a past or current infection [8][21]. Nonetheless, MAT is considered the immunological reference standard method for leptospirosis experimental diagnosis by the World Organization for Animal Health (WOAH) [22] and the WHO [23].

Another supportive immunological test for the detection of antibodies is enzyme-linked immunosorbent assay (ELISA) [24]. Although the diagnostic accuracy of ELISA has not been completely established [25], the facilities of performing ELISA (manipulation with killed antigens) rather than MAT (live antigens) shows a promising alternative to several laboratories in tropical countries which reported its high sensitivity and specificity [26][27].

In recent years, cases of human and animal leptospirosis have been reported in numerous countries in the Middle East through direct and/or indirect diagnostic techniques. Human cases commonly involve farmers, rice field workers [28][29][30][31][32][33][34][35][36], travelers [37], and plumbers [38]. Leptospirosis cases in children and/or adults in contact with infected livestock or contaminated water have also been reported [28][39][40][41]. However, cases without a clear history of pathogenicity [42] and those without obvious occupational activities known to be risk factors for leptospirosis transmission have also been noted in some Middle Eastern countries and are qualified as “inner-city related”. Moreover, cases of co-infection with both dengue fever and leptospirosis have been described in the Middle East [43]. Animal case reports normally include numerous species but mainly involve livestock. Furthermore, the direct detection of leptospirosis in water resources has been reported [44]. Preventive measures to reduce health and economic consequences following *Leptospira* infection in the community relies on a deep understanding of the epidemiology, public awareness, and vaccination of domestic animals and populations at risk. The knowledge of the predominant serogroup of a host is an important guide for an effective vaccination since the latter strategy only bestows a protective immunity restricted to homologous or closely associated serovars [45].

2. Epidemiology of Leptospirosis

To the best of our knowledge, this is the first research to summarize the prevalence and seroprevalence of leptospirosis and *Leptospira* infection in the Middle East. The disease, which continues to inflict a high burden worldwide, has been neglected in this particular region. From a broad perspective, almost all Middle Eastern regions reported information on the prevalence and/or seroprevalence of leptospirosis and *Leptospira* circulating serogroups. However, the prevalence values and serogroup distribution differed according to hosts and countries.

The prevalence and seroprevalence of leptospirosis in humans appear important in the Middle East, especially when compared with the prevalence and seroprevalence in other regions worldwide. Many leptospirosis outbreaks have been described in tropical and subtropical regions, including Latin America, Northern America, Southern Asia, and Africa, with some having incidence rates reaching 100 per 100,000 habitants per year [46][47][48]. However, to the best of our knowledge, a seroprevalence and prevalence of >41% have not been reported in these regions, despite having an adequate climate to support *Leptospira* survival and favorable human exposure. Indeed, the highest seroprevalence rates reported recently in Latin America were 40.2%, 23.6%, 8.8%, and 7.2% in Brazil, Peru, Colombia, and Ecuador, respectively [49]. In addition, the highest prevalence reported in Africa is 19.8% [46]. These results may be due to the sampling design being subject to selection bias by only reporting severe/laboratory-confirmed cases and/or hospital patients with acute febrile illness. Such a research design cannot provide an accurate presentation of leptospirosis cases because the disease is only known to cause severe complications in 5% to 10% of cases [50]. The reported prevalence and seroprevalence rates in the Middle East are higher (>42%) when either applying the same or different selection bias. This region not only reported acute cases

but also asymptomatic cases relevant to the controlled group and recorded higher seroprevalence than the previously cited regions [51]. For instance, Iran tested seroprevalence in both healthy and hospitalized patients and recorded values of 48.5% and 64.7%, respectively [51][52]. Therefore, the risk factors for acquiring the disease in the Middle East may be more important than those in other regions.

SSI combined with MAT was reported in the research as the indirect method of serogroup identification. The tests related have the advantage of identifying a particular serogroup using available reference strains for manipulation. Therefore, the host serum is exposed to a panel of serovars, and the results vary in a dependent manner. Various serogroups have been reported in the Middle East; however, these serogroups are unlikely to be exhaustive, given that they could have been expanded with the use of additional reference serovars. In the top five hosts (humans, rodents, goats, sheep, and cattle) of this region, the predominant serogroup was SJ in cattle; AUT in goats; and ICT in humans, sheep, and rodents. The predominance of each serogroup in each of these hosts has been commonly reported in the literature, except in the case of goats. Serogroup SJ has been the most commonly reported serogroup in cattle in different countries worldwide, including the United States of America, France, Ireland, the Netherlands, Belgium, and others [53][54][55][56][57]. The serogroup ICT is commonly reported in rats worldwide [58][59] and is known to be the major causative agent of leptospirosis in humans [60][61]. In sheep, the predominance of the latter (ICT) serogroup supports previous observations in other countries [62]. In the case of goats, the predominance of the serogroup AUT has not been reported regularly in other countries worldwide [63][64][65] but has been commonly reported in related publications in the Middle East. However, this result appears robust given that the number of MAT positive cases associated with AUT (n = 191) in goats was considerably higher than the expected serogroup SJ (n = 12), which is considered predominant in goats in other countries [66][67]. Nonetheless, local variation may have led to such results and, as this is the first epidemiological study in the Middle East, it may be an indication of the most predominant serogroup in goats in this region. However, this assumption should be consolidated or proven by further studies. Moreover, the preponderance of the serogroup ICT in sheep in the Middle East can be explained by the high probability of their infection by rodents (carrying ICT) or their capacity for selective carriage of some ICT strains, as described for other hosts (pigs) in the literature [2]. The predominance of the serogroup ICT in humans in the Middle East may be due to infection by cattle, sheep, and rodent carriers of this serogroup, during their occupational work (farmers, rice farmers), travel, or contact with contaminated water. It may also be due to the importance of pathogenicity caused by the latter (ICT) serogroup leading to leptospirosis susceptibility and, therefore, its diagnostic examination [1]. Despite the various biases within the collected data, data regarding the serogroups in the Middle East remain informative because the objective of this research was to describe the circulating serogroups regardless of their titers and MODs used. In addition, no records of human or animal vaccination were mentioned in the selected publications; therefore, the serogroups detected in the Middle East were not concluded according to antibodies developed by vaccination but by infection. Such results help orient the type of vaccine that will be regarded as effective to each host. For instance, protection against *Leptospira* serovar ICT and SJ through vaccination should reduce the risk of leptospirosis in humans and cattle, respectively. Nonetheless, the adequacy of the serogroup repartition in the Middle East may be questioned because of the possibility of cross-reactions, which may lead to the consideration of serogroups that are not actually present.

However, the distribution of the serogroups was analyzed at the whole population scale to minimize the effects of cross-reaction in results, as has been performed in previous studies [56][68].

As expected, the reported seroprevalence and prevalence differed according to studies, likely due to variability in the MODs of *Leptospira* spp. Some diagnostic methods, such as PCR or any other direct method, can only detect nucleic acids in the first week of the host infection, known as the bacteremia phase of infection [1]. However, other MODs, such as MAT, ELISA, or any other SSI, can detect antibodies days after the onset of the disease and for a much longer duration [27]. The difference in the time margin between the persistence of the bacteria and the antibodies in host tissues lessens the chances of prevalence reports, in contrast to the chances of seroprevalence reports.

Several studies have reported null prevalence and seroprevalence. For some studies, this can be due to the small sampling size (<30 samples), 26 goats [69], 22 camels and 14 horses [44], five sheep [70], two weasels [71], one cattle, and one dog [70], which may not indicate the true distribution of the infection in the geographic location. Moreover, the sampling size may not be sufficient to detect an infected or exposed host if present in the population; indeed, a sampling size of 26 individuals allows the detection of a minimum prevalence or seroprevalence of 11% [72]. In the case of Cyprus, the country did not state human leptospirosis cases for several consecutive years [73], except for the year 2003 when 0.3 cases of 100,000 habitants were infected [74]. However, the case definition may not respond to sensitive detection of the *Leptospira* infection given that many asymptomatic or moderate cases could be experienced by the host, including humans. The European Center for Disease Prevention and Control reports were sent in accordance with the case definitions established by the European Union that included Cyprus. The general principles for the application of the case definitions are to only report laboratory-confirmed symptomatic cases, while suspected cases were only regarded as cases if they revealed a clear clinical picture with a judicious laboratory diagnosis [73][74]. In addition, the 2008 case definition was restricted to pathogenic *Leptospira* spp., namely *L. interrogans*, whereas, starting in 2012, all pathogenic *Leptospira* spp. were considered in the detection panel [73]. Such pathogenic *Leptospira* species restrictions may lead to an underestimation of the incidence [74]. Moreover, a null seroprevalence was reported in cattle, goats, and sheep in Cyprus, and, to the best of our knowledge, only a few imported calves tested positive in 1983 [75]. However, one publication is insufficient to determine the seroprevalence of ruminants in Cyprus but could explain the possibility of acquiring such seroprevalence. Surprisingly, studies in Palestine reported a null seroprevalence in rodents, even with a high sampling number. This may have been due to the antibody response of the *Leptospira*-infected rodent, which is frequently found to be under the threshold of positivity [76][77]. It may also be due to the remarkable variation in prevalence and/or seroprevalence from one rat colony to another starting from 0%, as reported in previous studies [78][79]. Thus, the apparent seroprevalence in Palestine could be underestimated compared with the true seroprevalence of the tested rodents because the sampling concerns a limited number of colonies (n = 2). Although the seroprevalence is null in rodents, infections have been detected in Palestine in both humans (seroprevalence of 1.9%) [80] and cattle (seroprevalence of 8.5% and 9.5%) [80][81]. The apparent seroprevalence in both hosts was elucidated by co-researchers, who suggested that numerous outbreaks of leptospirosis in hundreds of cattle were the cause of human infection, such as those reported a few years prior to sampling [82][83].

Some countries have reported a remarkable seroprevalence range in the human population. The greater the number of studies combining various factors, such as the time interval between the two studies, the spatial variation, and the design of the study adapted in different publications related to the same country, the greater the seroprevalence variability.

An important time interval in the same country could lead to variations in disease epidemiology. For example, in Egypt, a seroprevalence of 0.5% was reported in 1957 [84], whereas a seroprevalence of 49.7% was reported in 2015 [44]. The risk factors for acquiring the disease depend on the environmental features and animal carrier abundance, which differ with the spatial variation, explaining such variability [85][86]. Therefore, spatial variability in the same country with a large surface area and an important distribution of studies throughout those areas, such as Iran, Turkey, and Egypt, could lead to seroprevalence variability. In addition, the lack of comparable design studies in the same host may lead to variable seroprevalence. The design of the study is specific to each publication because the sampling criteria were unique; some groups were chosen because of their tendency to be infected due to their occupations or professional activities, some were chosen randomly as controlled groups [87][88], and others were sampled for a differential diagnosis (cases of hepatitis, acute febrile illness for humans, and brucellosis for cattle) [89][90][91]. However, when the same type of group was chosen, low seroprevalence variability was observed. For instance, in the case of humans in Yemen, when only two publications targeting similar types of groups (people at risk) were reported, the seroprevalence ranged between 41.3% [92] and 42% [93]. The sampling period may also have had a major impact on the incidence of leptospirosis throughout the year because of the seasonal pattern of the disease and its recrudescence in specific seasons, in which the highest incidence occurs mainly in summer or/and fall in temperate countries and in rainy seasons in warm-climate regions [8]. Therefore, the seroprevalence can differ throughout the year in a particular country and within the same population. For instance, a study in the north of Iran (temperate region) demonstrated a higher prevalence of leptospirosis in individuals in autumn and summer compared with that in spring [94]. In summary, the greater the number of studies combining the latter factors, the greater the seroprevalence variability. Moreover, the more these factors vary between publications, the lower the comparability of the prevalence or seroprevalence.

The epidemiological knowledge of leptospirosis is unclear for some countries in the Middle East because of the type and content of publications. For instance, studies in Oman only reported case studies [37][40][43]; therefore, the magnitude of leptospirosis in Oman remains unknown. However, a high prevalence is expected due to the globalization of travel and trade, occupational activities, and the temperate climate of the country [95]. Other countries, such as Saudi Arabia and the United Arab Emirates, only reported a prevalence and/or a seroprevalence in a few hosts (camels and cattle) due to a greater interest in describing the health status of the mammals that are largely present in these countries. Epidemiological knowledge is also lacking in some countries in the Middle East due to the absence of studies. For instance, in the twenty-first century, Lebanon, Kuwait, and the Syrian Arab Republic did not renew their interest in studying *Leptospira* infection. This suggests that leptospirosis is not within the public health policy priorities and/or that its burden is underestimated; this is in contrast to that noted in other Middle Eastern countries, such as Iran, which continuously show their interest in studying the disease by attempting to revise and authenticate its detection methods [96][97].

The time interval between the reported publications, the difference in the spatial environment, the particular design of the study adapted, and the number of publications related to each country led to the cognizance of leptospirosis variable epidemiology in the Middle East. Therefore, heterogeneous strategies applied in each country and between different Middle Eastern countries should be limited as much as possible, and a harmonized strategy should be adapted for better comparison of epidemiological studies relating to the seroprevalence of leptospiral infection.

- For the detection methods, PCR and culture should be prioritized for direct detection and MAT and ELISA for indirect detection. These methods can be applied in parallel when sampling particular hosts, whereas their efficacy can be limited to others. For instance, direct methods should be prioritized in the case of rodents because they have a low antibody response to leptospiral infection [76].

- As MAT remains the reference detection method, a minimum and common panel of serovars from selected serogroups should be included in all Middle Eastern countries that require shared reference strains. The minimum number of serogroups that should be tested are ICT, GRIP, SJ, CAN, AUT, and POM.

- A common human case definition should be a reference to all Middle Eastern countries to report the maximum, confirmed, and suspected number of clinical cases of *Leptospira*. Random sampling could be performed to describe the epidemiological situation in humans more comprehensively, considering asymptomatic or moderate cases.

- For the surveillance of *Leptospira* infection in domestic animals, an analysis of data on a continuous basis following diagnostic examinations in veterinary laboratories should be considered to determine the distribution of *Leptospira*. Such data should be communicated to the organizations and the public, indicating the applied diagnostic method of examination. Moreover, the sampling modalities should be stated by the community of veterinary practitioners in order for them to be interpreted at the Middle East region level.

- Veterinary practitioners should be encouraged to provide all available information on animals and herds to enable a good diagnosis and improve epidemiological analyses. Information on the reason for examination, and the farms, herds (size and type), and animals (age, sex, clinical status) at diagnostic testing will facilitate improved epidemiological analysis and the ability to suggest risk factors to move toward more efficient risk-based surveillance in the future.

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