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Leptospirosis – current risk factors connected with human activity and the environment

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Abstract

Leptospirosis is a widespread although recently neglected zoonosis recognized worldwide. The disease seems to be underestimated, especially in countries located in the temperate climatic zone. The presented article concerns the main characteristics of leptospirosis and describes formerly known and recently observed environmental, occupational and recreational risk factors significant in the spreading and pathogenesis of the disease. The aspects of epidemiology significant in the temperate climatic zone are emphasized. The majority of cited articles present cases of the disease reported from Europe or North America. Climatic changes (warming) and extreme weather events such as floods are potential risk factors of leptospirosis. Also, some socio-economic phenomena, such as the intensive migration of people resulting in the transfer of the infections acquired in tropical countries, or worsening of economic status in the cities, increase the probability of disease. Apart from the danger connected with rodents, which are the main vectors of leptospires, occurrence of the disease in dogs and cats can generate a higher risk of infection for humans. Infections may also be acquired during various types of agricultural work and during recreational activities, such as swimming. The results of recent investigations show that ticks are also potential vectors of leptospires. The more frequent emergence of leptospirosis in countries located in the temperate climatic zone emphasize the need to verify knowledge related to the risk of its appearance, and to consider this disease during diagnostic processes.

Key words

leptospirosis, epidemiology, risk factors

INTRODUCTION

During the last few decades, leptospirosis has become seriously neglected, especially in countries located in the temperate climate zone. The main reasons for this situation are probably: 1) a relatively low number of cases noted in humans and animals living in the temperate climate zone; 2) established, quite effective methods of therapy and prevention of the disease; 3) seemingly well-determined epidemiologic situation concerning the disease. However, more recently, many reports and reviews indicate leptospirosis as a re-emerging, widely spread zoonosis globally. According to Hartskeerl et al., [1] leptospirosis poses an increasing public health problem worldwide, as evidenced by markedly increasing incidence rates and multiple outbreaks on all continents. The estimated incidence of about half a million severe human cases annually is probably an underestimation, while the burden for animal health is unknown.

The natural foci of leptospirosis occur usually in swampy areas [2, 3, 4]. Higher morbidity can be observed in countries or regions (areas) with a higher proportion of surface fresh water (lakes, rivers, developed canal systems, etc.) [5, 6]. In the tropical climatic zone, where environmental conditions are most favourable for survival of leptospires and the highest morbidity is noted, extreme weather events such as cyclones and floods occurring in recent years with increasing frequency and greater intensity, may potentially result in an upsurge in the disease incidence, as well as the magnitude of leptospirosis outbreaks [7, 8]. It was estimated in Brazil, that for each millimeter increase in maximum daily rainfall for the month above the average for the period studied, there was an increase of 0.55% in the number of leptospirosis cases relative to the average for that period [9].

In the temperate zone, climatic changes (warming) can potentially be one of factors increasing the probability of leptospires survival in the environment. Other factors facilitating spread of infections caused by *Leptospira* in the temperate climate zone are some socio-economic phenomena, such as the intensive migration of people, resulting in the transfer of infections acquired in tropical countries [10], or changes in economic status of individuals (becoming poor, homeless) or some communities (poor or depopulated quarters of cities), the consequence of which can be lower hygiene status and infections transmitted from rodents [11]. Apart from the danger connected with rodents, which are the most important reservoir of leptospires and a source of infections for other groups of animals and for humans [2], new phenomena concerning the etiology of leptospirosis in some species of domestic animals (dogs, cats) can generate a higher risk of infection for humans [12, 13]. Otherwise, some reports from recent years also describe cases of human leptospirosis connected with sources of infection already known for many decades (e.g. infections acquired during agricultural work) [14]. This is evidence of a serious hazard caused by the disease, in spite of better protection during work and a generally higher level of hygiene then in previous decades.

The low occurrence of leptospirosis observed in the temperate climate zone and a protean the nature of the disease connected with many unspecific signs, can cause

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significant difficulties in making an accurate diagnosis. The diagnostic problems and lack of systematic, adequate monitoring of leptospirosis in many countries, can result in incomplete knowledge concerning the prevalence of the disease and can cause underestimation of the real risk connected with the spread of infections caused by *Leptospira* spp. The aim of the presented study was to briefly reiterate the most important characteristics of leptospirosis, and present currently observed leptospirosis risk factors connected with various types of human activity and with the environment.

Course of the disease. In humans, typically a biphasic course of leptospirosis is often observed. The manifestation of signs is preceded by an incubation period lasting usually 1–2 weeks (range: 2–30 days). The first phase of the disease, lasting up to 7 days, is connected with a period of leptospiremia (the presence of leptospires in the blood). Unspecific signs, like fever, chills, headache, myalgia are observed during this phase. More rarely, conjunctivitis, maculopapular skin rash and sporadically icterus can be noted. After 5–7 days, the signs can retreat and disappear. In some cases, the patient can recover (sometimes without medication) or the disease can regress to a subclinical form, but usually, after 1–3 days of apparent remission, the second phase of the disease begins. This is a consequence of leptospires transfer from the blood vessels to the organs. The disease in this phase can be categorized into icteric or anicteric form. The anicteric form is milder and diagnosed more often (approximately 90% of cases). The signs of meningitis (headache, neck stiffness) are most often observed in this form. Sporadic cases of encephalitis are also noted. In some patients, uveitis may develop which can appear some weeks or even years after the onset of the disease [15].

The icteric form of the disease is a consequence of serious hepatic, renal or pulmonary disorders caused by leptospires located in these organs. Apart from jaundice, the changes in aminotranspherases activity, the presence of leucocytes and erythrocytes in urine, albuminuria, the increase of urea and creatinine levels in blood, oliguria and anuria can be observed in this form of leptospirosis. Signs of the anicteric form (mentioned above) connected with the nervous system are also sometimes noted in the icteric form.

Recently, severe haemorrhagic pneumonia related to acute respiratory distress syndrome has been seen in the anicteric form [16]; however, it is not always associated with leptospirosis infection.

Infections in pregnant women caused by leptospires, can result in various disorders of foetuses and often their death. However, administration of appropriate antimicrobial agents can result in the birth of healthy infants [15, 17].

One of the troublesome and difficult to eradicate consequences of *Leptospira* infection is the renal carrier state, which can last for many months or sometimes for years.

A mild form of leptospirosis seldom leads to death; however, in severe forms (diagnosed in 5–10% of patients), mortality can reach 5%–40% [18, 19].

The molecular pathogenic mechanisms of leptospirosis are not entirely clear at this time. Several candidate virulence factors have been identified that might contribute to the pathogenesis of *Leptospira* infection and disease, including lipopolysaccharide (LPS), hemolysins, outer membrane proteins (OMPs) and other surface proteins, as well as adhesion molecules [20]. Comparative genomics of pathogenic and saprophytic strains of *Leptospira* has allowed the identification of more than 900 genes unique to either *Leptospira interrogans* or *Leptospira borgpetersenii. T*hese genes potentially encode virulence-associated proteins. Most probably, leptospiral virulence genes do not have homologues in other bacterial species, and *Leptospira* possesses a unique virulence mechanism [21].

Risk factors and epidemiology. In spite of the relatively high ability of adaptation for various environmental conditions in the temperate climate, leptospires can find optimal possibilities for survival in warm-blooded organisms, mainly in mammals. Evidence for the carriage of *Leptospira* has been found in virtually all mammalian species examined [22]. The renal carrier state of rodents still remains a basic factor for the possible survival and spread of of leptospires. The primary source is the excretor rodent, from whose proximal renal tubules leptospires are excreted into the environment with urine. Although they are susceptible to environmental factors, in particular drying, they can survive for long periods in water and wet soil [8].

Additional important factors are suitable environmental dampness and sufficient temperatures. Well-described cases of leptospirosis, exemplifying typical ways of infection and illustrating the importance of the above-mentioned factors have been diagnosed in Germany in the summer of 2007 [14]. The cases were noted among seasonal strawberry harvesters from Romania, Slovakia and Poland, and employed on a farm situated in the region of Dűren, North Rhine-Westphalia. The etiological agent of the disease appeared to belong to the species *Leptospira kirschneri* serovar Grippotyphosa. The infection was transmitted from mice which were found in large numbers on the plantation. Additional favourable factors for infection transfer were the temperature: all disease cases were noted between June – August 2007; 10 days before the outbreak the mean daily temperature ranged from 18.4–23.1 °C; abundant rainfalls (spring 2007 was the wettest since 1991, and 10 days before the outbreak of the disease the average daily rainfall in the region of Dűren was 10.5 mm).

Workers employed in agriculture belong to professional groups mostly threatened by leptospirosis. Individuals working directly with animals (farmers, cowherds, veterinarians, abattoir workers, etc.) can acquire the infection by contact with contaminated urine or working in pens contaminated by infected urine, during milking, after animal bites, after contact with aborted fetuses or parts of placenta, and infected carcasses (also during the carving of slaughtered animals in abattoirs) [23, 24, 25, 26, 27, 28]. Krawczyk [29] in his investigations in northern Poland found 13.8% of seropositive reactions among the rural inhabitants exposed to direct contact with animals and 1.5% among those without such contact. A serological survey described by Spanish investigators of 197 persons employed in agriculture indicated positive results in 21% [30]. The highest percentages of positive results were noted in the subgroups of cray-fishers, rice-workers and butchers. Furthermore, the professions connected with the possibility of exposure to direct or indirect contact with rodents, mainly with rats, are threatened by infection. This group includes, among others, individuals working in sewer systems, miners, hunters, foresters, soldiers, rodent control workers, people working in fish farms, storehouses and harbours, in piggeries, cowsheds, etc. [29, 31, 32, 33, 34, 34, 35, 36, 37].

The threat connected with transmission of leptospires from rodents to humans can be of concern to some social groups, such as the homeless or inhabitants of poor suburbs or depopulated quarters of cities. Leptospirosis is regarded as an important disease in European regions of poverty [38]. According to Cruz et al. [39], leptospirosis has disseminated from its habitual rural base to become the cause of urban epidemics in poor communities of industrialized and developing nations. Serological investigations carried out among the inhabitants of Baltimore in the USA indicated positive results in 16% of examined people [40]. In another study, also carried out in Baltimore, leptospires were detected in 19 of 21 trapped rats [11]. A serological survey of children living in clean quarters of Detroit in the USA showed 30% of positive results [41]. The investigation of rats from the same city revealed positive results in 77% of examined serum samples.

Detailed studies carried out in Switzerland on the prevalence of *Leptospira* infections in urban populations of 4 species of rodents showed, depending on the species, 10%-20% positive results [42]. In Germany, a study on rats was conducted in 16 urban regions [43]. DNA of *Leptospira* was revealed in 19% of investigated kidney samples. Serological surveys of rats trapped in one of the major Polish agglomerations in Wrocław, Silesia, revealed the occurrence of antibodies reacting with serovars Icterohaemorrhagiae, Canicola, Hebdomadis and Sejroe [44]. The prevalence of leptospiral infections among rural populations of rodents has been previously studied many times in various European countries [45, 46].

Some new epidemic aspects related to a real risk of Leptospira transfer to humans were observed recently in pet animals. Acute leptospirosis in dogs is known as Stuttgart disease. For a long time, dogs were recognized as a reservoir of leptospires and a potential source of infection. However, they were usually infected by serovars Canicola and Icterohaemorrhagiae. These two serovars have been routinely used as antigens in vaccines for dogs. The vaccines quite effectively prevented transfer of these two serovars to humans. Some reports have appeared in recent years in North America [12, 47] and in Europe [48, 49], however, informing of more frequent infections caused by serovars like Autumnalis or Pomona which have seldom been found previously in dogs. These new serovar antigens are still not often included in vaccines for dogs, which enables the development and transfer of infections also in cases of 'vaccinated' dogs. The immunity generated by standard vaccines against leptospirosis is effective only in the case of serovars, for which antigens are included in the vaccine. Vaccinated dogs with these unsuitable preparations are an especially high risk to humans. The transfer of leptospires from dogs is also indicated as one of the most important causes of human leptospirosis during the last two decades in Russia [50].

Another source of infection recognized in recent years seem to be cats. Until recently, they were regarded as not very sensitive tor infections caused by *Leptospira*. There were almost no observed signs of infection or antibodies for *Leptospira* among cats. However, French investigators examining a group of 98 sick cats found that 48% of them presents with antibodies for *Leptospira* sp. [13]. Admittedly, until now there have been no results revealing the scale of human infections caused by leptospires acquired from cats, but the mentioned results seem to indicate quite a high risk of this transfer.

A particular type of animals increasingly treated as pets, are rats and mice. The risk of infection in these cases depends on the source from which the animals come, and on the efficacy of their isolation from potential sources of leptospires from the environment.

Many reports provide information concerning the prevalence of Leptospira infections among various species of domesticated animals, e.g. cattle [51, 52, 53], swine [54, 55], sheep [56, 57], horses [56, 58, 59], etc. The majority of these animals are based on the results of serological findings. Although some of the positive serological results can be evidence of contact only with *Leptospira* (there is no proof of current infection), the results of the above-mentioned investigations among workers employed in agriculture [32, 33, 34, 36, 37] can confirm a high risk connected with animals being potential sources of infection.

An additional factor for the potential risk of transmission of leptospires from animals to humans is penetration of urbanized areas by wildlife species which live in city suburbs. The quick development of agglomerations and occupancy of uninhabited (often woody) until recently areas can create new behaviour in animals connected with easier food availability. Wild boars, foxes, deer, martens, beavers, and in North America, e.g. skunks or raccoons, can be met quite frequently not only in suburbs but sometimes in long established urbanized quarters. The natural environment niches of these animal species can often demonstrate suitable conditions for the survival of leptospires, which makes highly probable their transfer through animals to the urbanized areas. Serological screening of wild boars living in the suburbs of Berlin showed 18% of positive results [60]. Another serological survey carried among wild boars in Germany indicated 24% of positive results [61], and similar screening in Poland showed 25% of positive reactions [62]. A serosurvey among foxes carried out in Germany indicated 2% positives [63].

The problem of the role of ticks and other parasitic arthropods in the transmission of leptospires has not been addressed for a long time. Over 50 years ago, Burgdorfer [64, 65] experimentally demonstrated the transmission of *Leptospira pomona* by argasid and ixodid ticks. At the same time, Krepkogorskaya and Rementsova [66] isolated two strains of *Leptospira grippotyphosa* from 35 homogenates of *Dermacentor marginatus* ticks collected from cattle in Kazakhstan. Recently, Wójcik-Fatla *et al.* [67] found by the PCR method the presence of the *Leptospira* spp. DNA in 10.5% of examined specimens of *Ixodes ricinus* collected in eastern Poland. The infection rate was much greater in the area exposed to flooding compared to those not exposed (15.5% vs. 1.4%, $p<0.0001$). The prevalence of *Leptospira* spp. in nymphs (16.9%) was two-fold greater ($p<0.01$) than in females and males (7.9% and 7.1%, respectively). These results suggest the possibility of the dissemination of leptospirosis in large populations of humans and warm-blooded animals exposed to tick bites.

For many decades, leptospirosis was thought to be primarily an occupational disease; however, in the temperate climatic zone an increase of recreational exposure incidences has been observed recently [68]. The highest risk is associated with exposures occurring in water sports [69]. Many of these types of infections appear in athletes practicing the triathlon. The swimming part of the competition is usually organized in

rivers or lakes where water contaminated by leptospires can be a source of infection for triathlets. Cases were reported in the USA [70], Germany [71, 72], Austria [73] and Ireland [74].

An example of similar types of infections, acquired in tropical countries, was a well-described case of leptospirosis diagnosed in participants of the multi-sport endurance race Eco-Challenge-Sabah 2000, organized in Malaysian Borneo in the end of September 2000. The majority of participants came from North America and Western Europe. After the climbing event, caving, mountain biking and long-distance jungle trek, during which many of the athletes suffered injuries and various skin lesions, the group swam prolonged distance in the Segema river. During the swim, many of the participants (at least 42%) were infected by leptospires [75].This presents an example of recent frequently-noted leptospiral infections transferred by tourists returning from tropical countries to the temperate climatic zone [10, 76].

Outbreaks of leptospirosis in swimmers are still being noted in European countries. One such case was reported in France in July 2011 when an infection was acquired by two swimmers in Lake St Jean de la Porte in the Rhone Alps region [77].

Waterborne leptospiral infections have also been noted in persons practicing kayaking, rafting, fishing [78, 79, 80], etc. An interesting case was the diagnosis of leptospirosis in cavers, who acquired the infection when crossing underground streams probably contaminated by rodent urine [81].

An outbreak of leptospirosis among boys attending a scout camp was reported in Belgium in August 2012. The camp was located on the bank of the Semois river in the province of Luxembourg. From a group of 25 participants, 10 boys developed clinical signs and 3 of them were hospitalized. Leptospirosis was confirmed serologically in all hospitalized patients. Wildlife (rats) were suspected as the source of infection because it was suspected that the boys had been playing with a rat. The suspicion was confirmed during investigations of rats captured from nests in the vicinity of the camp. Pathogenic leptospires were found in kidneys and livers of the captured animals and antibodies against *Leptospira* spp. were found in their body fluids [82].

According to Jansen et al. [5], of 102 human laboratory-confirmed cases of leptospirosis in Germany between 1997–2000, 30% were related to occupational exposures, 30% to recreational exposures (including traveling abroad in 16%), and 37% to residential exposure. Direct contact with animals, mostly rats and dogs, was observed in 31% of the cases. The authors concluded that recent changes in transmission patterns of leptospirosis, partially caused by an expanding rat population and the resurgence of canine leptospirosis, may facilitate the spread of the disease in temperate countries like Germany.

The environmental risk factors associated with leptospiral infections mentioned above are cumulated during floods. The water rinsing microbiological contaminations and floating drowned animals (including rodents) from flooded areas become a source of infection and the vector transferring the microbes. Water-soaked soils can create advantageous environmental conditions for leptospires for a long time after the flooding. Although in temperate climatic zones leptospires survive in the environment for a much shorter time than in tropical countries, there are data that show a higher leptospirosis morbidity after floods in some European countries. This was observed, e.g. in the Czech Republic and in Poland after the huge floods in 1997–2002 [83, 84]. According to Zitek and Benes [83], the rates of reported and serologically confirmed cases of leptospirosis after these floods in the Czech Republic were three times higher than usual, with the specific morbidity reaching 0.9 case per 100,000 population.

The environmental, occupational and recreational exposure risk factors associated with leptospirosis mentioned in this article, modulate the epidemiologic situation of the disease and risk of infection worldwide. Many more articles and books which have not been quoted in the presented study, describe the role and significance following these factors in the tropical climate. However, the aim of this study was to summarize what was known previously and to indicate recently revealed risk factors significant in the transmission of leptospiral infections in the temperate climate zone. The efficacy of recognition, treatment and control of the disease requires adequate knowledge concerning its epidemiology. The recently observed increase in the frequency of leptospirosis in the temperate climate zone obliges us to verify the risks connected with its appearance and to take the disease in consideration more often in the diagnostic process.

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