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Leptospirosis in the Republic of Korea: Historical Perspectives, Current Status and Future Challenges

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Leptospirosis is an important public health problem in the Republic of Korea (ROK), occurring sporadically or in outbreaks during the autumn season. Wild rodents, *Apodemus agrarius*, have been mainly involved in human leptospirosis. The majority of carrier animals are infected with *Leptospira interrogans* serovar *lai*. The characteristic pulmonary involvement or hemorrhage may increase the clinical severity or result in fatal outcomes, and these aspects continue to be a threat to people in endemic areas. While the disease incidence has been relatively low in recent years, there have been newer findings of livestock (zoo animals and racing horses) and rats (*Rattus norvegicus*) captured in urban environments as potential animal carriers. Many avenues of research are still open to define current changes in ecology, epidemiology, and the disease burden in both humans and animals in the ROK, together with global warming and climate change issues. In addition, national policy regarding the weighted wildlife monitoring system and the enhanced disease surveillance program is required to facilitate better monitoring and understanding of this disease.

Key Words: *Leptospira*, Epidemiology, Reservoirs, Pulmonary hemorrhage

Introduction

Leptospirosis is one of the well-recognized zoonotic diseases in the Republic of Korea (ROK), together with hemorrhagic fever with renal syndrome (HFRS) and scrub typhus, which are prevalent in rural areas during the autumn season. Wild rodents (*Apodemus agrarius*) are known as the primary natural reservoir for these different pathogens, *Leptospira interrogans*, hantaviruses, and *Orientia tsutsugamushi*. People who are exposed to the source of infection directly or indirectly have generally contracted the diseases in endemic areas.

Historically, HFRS had been recognized during the Korean War in 1951 [1, 2]. Leptospirosis was newly identified in late 1984 [3, 4], followed by identification of scrub typhus or tsutsugamushi disease among Korean patients in 1986 [5, 6]. With the availability of serologic tests for these agents, many sera from patients with suspected HFRS in 1985 and 1986 turned seropositive for leptospirosis and scrub typhus. Thereafter, it became clear that many cases of leptospirosis and scrub typhus might have been misdiagnosed as HFRS on the

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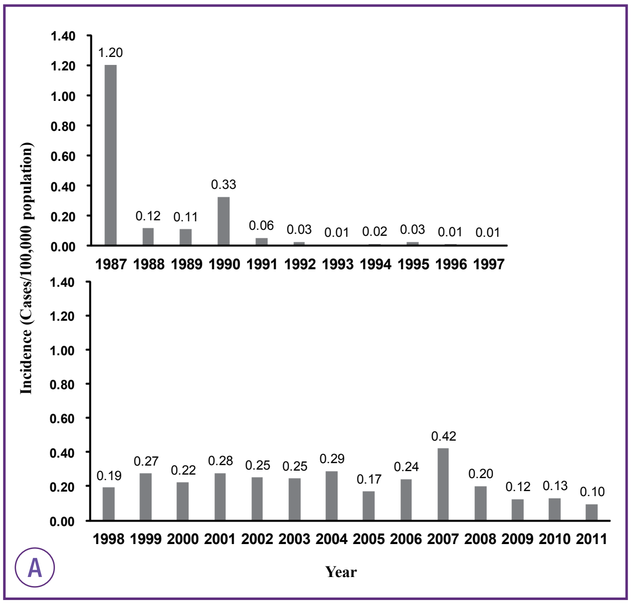

basis of clinical findings alone, because clinicians were unfamiliar with these diseases [7].

Leptospirosis, scrub typhus, and HFRS share a number of common clinical and epidemiological characteristics, including the epidemic season and several clinical features such as capillary leakage, thrombocytopenia, hemorrhages, and alterations in renal function. Serologic tests are the mainstay in differential diagnosis. However, the acute febrile patient living in an endemic area may have residual antibodies to more than one of these agents from previous exposures or possibly from mixed infections, collectively referred to as “leptangamushi diseases” in this country, which can often cause confusion in the clinical diagnosis. A great deal of work involving seroepidemiological surveys of acute febrile patients as well as wild rodents was undertaken for the three diseases from

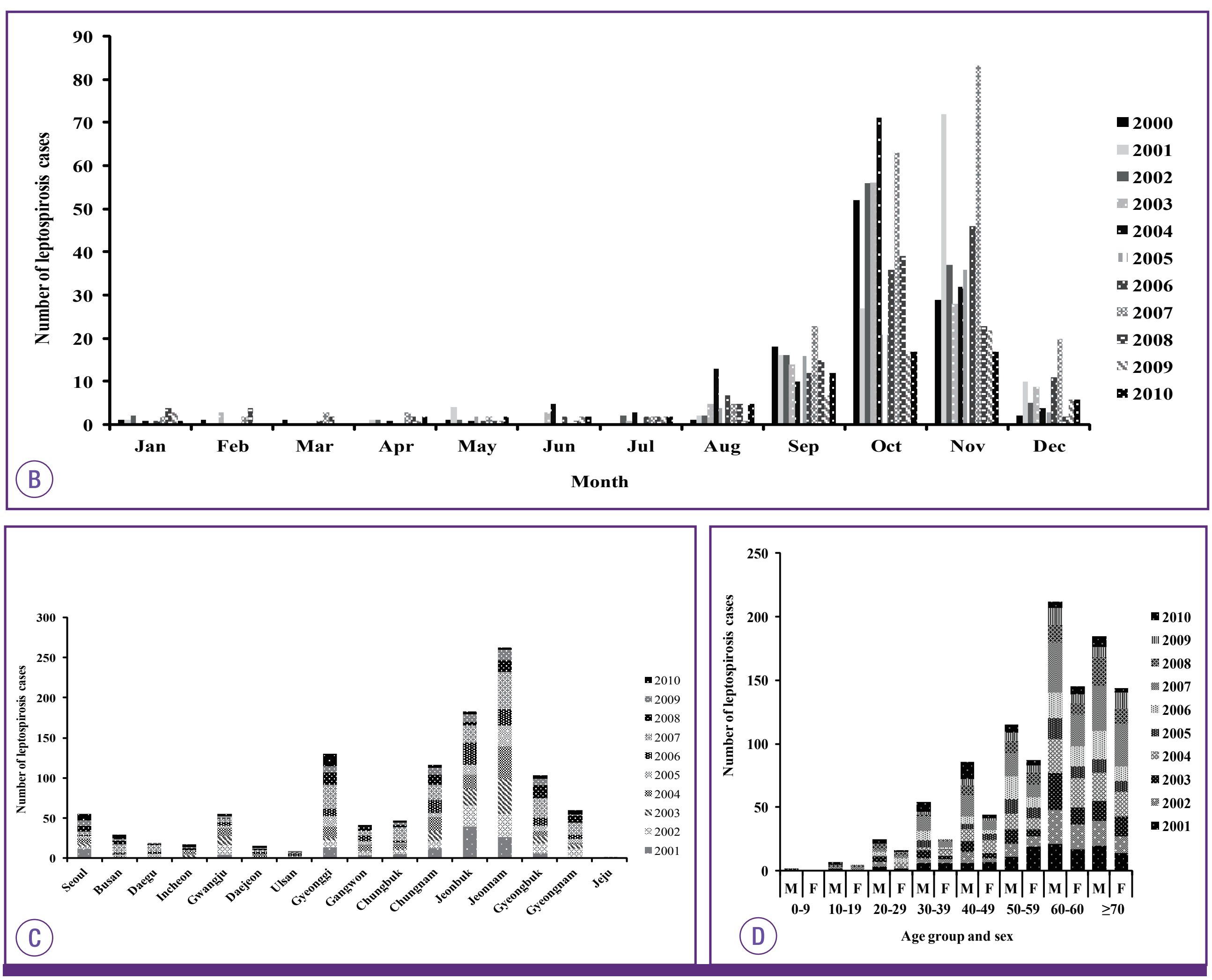

Figure 1. Incidence of leptospirosis (1987- 2011) and seasonal and regional distribution of the reported cases in the Republic of Korea (2001-2010). A: Annual incidence by years with or without leptospiral vaccination (1988-1997 and 1998-2011). B: Number of cases in different months. C: Number of cases in different regions. D: Number of cases in different age groups and sex. (Data source, the National Notifiable Disease Surveillance System from the Korea Centers for Disease Control and Prevention)

the mid 1980s through the late 1990s by Korean research institutions. In 1988, the Korean government introduced supplementary immunization activities against leptospirosis epidemics, and the reported cases of leptospirosis have gradually decreased since then.

While increasing antimicrobial resistance has received a great deal of attention as a serious global problem in the 21st century, the frequent and often dramatic appearance of new infectious agents or the reappearance of well recognized zoonoses continue to be threats to public health. Considering the persistence of animal carriers, the complex biology of the microorganisms, and changes in human behavior and climate, leptospirosis still has the potential to have a major impact on public health.

This paper reviews the historical and present status of leptospirosis in the ROK and describes new information from recent studies and the current challenges posed by the disease.

Leptospirosis

Leptospirosis is a worldwide zoonosis, caused by leptospires. Leptospires are gram-negative spirochetes. Pathogenic leptospires (*L. interrogans*) have been divided into 23 serogroups on the basis of serological cross-reactivity, with subdivision into 223 serovars [8]. On the other hand, the genetic classification by DNA relationships decided recently that the 13 pathogenic *Leptospira* species belonged to previously described genomospecies 1, 3, 4, and 5, with more than 260 serovars depending on characterization of epitopes of the lipopolysaccharide antigens [9]. A wide range of wild and domestic animals, especially rodents and small marsupials, cattle, pigs, and dogs are known as natural reservoirs. The infected animals chronically shed leptospires in their urine and contaminate natural environments. Human leptospirosis varies in severity from a mild influenza-like illness to a disease with a rapidly fatal course, with renal failure, jaundice, and hemorrhages. The severity depends on the type of leptospire, the size of the infective dose, and host factors [10]. Geographical, climatic, demographic, social, and cultural factors may affect the ecology of human, animals and leptospires [11]. Therefore, local information on these factors needs to be considered in reviewing the pattern of leptospirosis for an area.

Historical perspectives

In the ROK, human leptospirosis was newly identified in 1984 as the cause of the so-called "epidemic pulmonary hemorrhagic fever," a new clinical syndrome of unknown etiology that had been reported sporadically since the first noticed disease epidemic in the fall of 1975.

In the 1975 epidemic, the new syndrome that was characterized by bloody sputum or hemoptysis and abnormal chest X-ray findings following fever, chills, headache, and malaise occurred mainly in rice field workers in Gyeonggi and Chungbuk provinces. Detailed clinical and microbiological studies were performed extensively by clinicians and scientists, but they failed to identify the etiologic agent [12-20]. Meanwhile, a retrospective study had reported the occurrence of the syndrome before the 1975 epidemic as the potential endemic disease [21]. During the 1984 epidemic, Kim et al. derived and selected leptospiral infection as the hypothesized cause based on the epidemiological characterization of the disease [22], followed by successful isolation of leptospiral organisms from patients and wild rodents [3, 4]. Considering the 10-year delay in identifying the disease, it is instructive to note the importance of a systematic approach with multidisciplinary collaboration. In particular, researchers might be vulnerable to criticism regarding lack of scientific communication with neighboring countries such as Japan and China, where leptospirosis has been well documented for several decades.

Serovar determination of the new isolates often requires complex laboratory processes, including production of antiserum or monoclonal antibodies to the new strains and laborious cross-absorption serological tests comparing the known reference strains and reference sera. There had been difficulties in identification of the Korean isolates in earlier studies [23, 24]. In subsequent years, 102 isolates from patients and wild animals (mainly, wild rodents) between 1984 and 1996 have been identified as serovar *lai* (n=88, 86.2%), serovar *canicola* (n=2), and two new serovars (*yeonchon* and *hongchon*) [25-27].

There have been several outbreaks reported between 1984 and 1999 in the ROK: 1984 (-200 cases), 1985 (264 cases), 1987 (562 cases), 1990 (129 cases), 1998 (90 cases), and 1990 (130 cases). The epidemiological characteristics of leptospirosis have been described from investigations on the reported outbreaks in 1984, 1985, and 1987 [28, 29]. The largest 1987 epidemic involved five provinces (Jeonnam, Jeonbuk, Gyeonggi, Gangwan, and Chungbuk). The distribution of outbreaks was characterized by geographical and topographical conditions such as cultivated lands with terraced paddy fields located near hills. The pattern of occurrence showed a strong seasonality from September to November in association with severe floods, heavy rainfalls, or typhoons before the harvest season. Localized torrential downpours with 200-300 mm and 100-200 mm of daily precipitation were recorded in the 1984 and the 1987 epidemics, respectively. The majority of cases were farmers and their family members who had worked in the wet and muddy rice paddies. Many of them worked with bare hands and feet to repair damaged fruit-bearing rice plants following the floods. Several military personnel who participated in the group work to provide humanitarian aid had the illness, suggesting exposure to a common environmental risk or activities for a relatively short period. The wild rodents known as the main reservoirs are common to forests and fields. The isolation rates of *L. interrogans* from wild rodents captured in endemic areas were 15.5% in 1984, 14.9% in 1985, 1.6% in 1986, and 30.9% in 1987 [30]. Climatic factors such as floods and heavy rainfalls might play a part in the alteration of rodent inhabitation and the intensity of infection among them, affecting the numbers of leptospires and the chances of transmitting infection to people. The average temperature around the harvest season ranged from 15°C to 27°C, which could provide conducive conditions for leptospiral growth. These factors might offer the ideal environment for the seasonal outbreaks [28].

Leptospirosis was designated as a notifiable disease in March 1987, since the outbreaks had impacted public health significantly and had resulted in socioeconomic losses in the affected communities. From 1987 to 1991, the annual morbidity rate was estimated to be 0.3-1.2 cases per 100,000 population in the years with an outbreak, and 0.11-0.05 cases per 100,000 population in the years with no outbreak [29]. In a surveillance study performed in a rural community, the attack rates of serologically confirmed leptospirosis during the epidemic season in 1989 and 1990 were estimated to 1.12-3.35 and 3.63-9.85 per 10,000 persons (projected to population of the country), respectively [31].

Serological results inferred from the microagglutination procedure were used to evaluate variation in the incidence of the disease as well as the evolution of the *Leptospira* serogroups involved in the human disease. The seroprevalence rates among patients with acute febrile illness were reported as 11.2% (128/1141) in 1986 and 12.4% (219/1773) in 1987, followed by a gradual decrease to 4.9% (86/1761) in 1988 and to 0.2% (7/4,520) in 1991. Serum samples from 1986 and 1987 were frequently reactive to serogroups Canicola and Icterohaemorrhagiae. Male subjects outnumbered females in a ratio of 2.2:1, and the seropositivity rate for individuals over age forty was over 50% [32]. However, the seroprevalence has limits for estimating the magnitude of acute infection, as leptospiral agglutinin antibodies are detectable in about two-thirds of patients from one week of illness, frequently coinciding with the initial declining of fever, and then persist over several months [33].

Leptospirosis is an acute, self-limited disease of short duration, characterized by the abrupt onset of fever, chills, myalgia, and headache, accompanied by gastrointestinal symptoms and cough with or without hemopytsis. The clinical manifestations and severity vary greatly, from a flu-like illness to severe renal and hepatic failure, myocarditis, hemorrhage, and death (Weil's disease), depending on the inoculum dose, virulence of the infecting serovar, host susceptibility, and the organ systems predominantly involved. Based on the main clinical manifestations of serologically proven cases reported in the ROK, a characteristic pulmonary involvement in the early stages of the illness was observed in approximately 40% of cases. Three radiographic patterns for leptospirosis of the lungs have been described [34]. In patients who had massive hemoptysis, fatal outcomes resulted due to asphyxia or acute respiratory failure, especially in cases complicated by thrombocytopenia. In the majority of patients, the illness was mild and recovery occurred within one to two weeks with treatment. Case fatality was 2% to 12%, due to massive pulmonary hemorrhage and Weil's disease [28, 35-37]. While lung involvement has been described in anicteric leptospirosis with varying frequency in the old literature [38], pulmonary hemorrhage has been increasingly recognized worldwide to have a major impact on disease outcome in recent years. Mortality is higher in severe pulmonary hemorrhagic syndrome than in Weil's disease (>50% and >10% respectively) even when optimal treatment is provided [39]. Their pathogenic mechanisms, however, are still under investigation [40].

In 1988, the Korean government introduced immunization against leptospirosis as a supplementary immunization activity. The inactivated vaccine was produced with a local strain and was given to people in rural communities, with booster vaccinations every 6 months. The immunization activity was discontinued in late 1997 [41].

Current status and future challenges

According to the data of the National Notifiable Disease Surveillance System from the Korea Centers for Disease Control and Prevention (KCDC) (http://is.cdc.go.kr/nstat) [42], the incidence of leptospirosis dramatically decreased between 1991 and 1997 (average annual incidence, 0.02/100,000 population) even in the endemic areas, but has increased since then. From 1998 to 2011, there were 1,528 reported cases, and the average annual incidence was 0.22/100,000 population. No fatal cases were reported to the system, but case fatality rates from 2 individual studies were 5.8%-8.3% [43, 44]. No outbreak was evident by year. Most of the reported cases were from the endemic areas such as Jeonnam, Jeonbuk, Gyeonggi-do, and Chungbuk. Eighty-two percent of the reported cases were clustered in the period between September and November. Among the cases reported from 2001 to 2010, males outnumbered females in a ratio of 1.5:1 and individuals over the age of forty accounted for 88.3% of subjects (Fig. 1).

The current incidence in the ROK is lower than that in other countries in the Asia-Pacific region, including China [45]. However, the true incidence is likely underestimated, as full serological testing is not always performed for patients with acute febrile illness. The reason for the decreased incidence of leptospirosis from 1991-1997 has not been evaluated. Several factors such as the carrier animal population, climate factors, host immunity, or socioeconomic factors are considered to play a role in the dynamics of leptospirosis. In particular, the carrier state of reservoir animals is central to the persistence and epidemiology of leptospirosis. In a study on field rodents from endemic areas during October-December 1996, 12.6% of rodents (*A. agrarius*) examined were infected with serogroup Icterohaemorrhagiae serovar *lai*. However, this data did not significantly differ from that found in a previous study conducted in 1984-1987 [46]. In contrast, seroprevalence studies screening acute febrile patients for leptangamushi diseases reported low seropositivity rates for leptospirosis (0.5%-1%) from 1994 to 1998. [47-49]. Although the effectiveness of vaccination against leptospirosis has not been independently evaluated in the ROK, nationwide immunization activities could be a possible factor, based on unchanged reservoir carrier rates and the remarkable decrease in disease incidence during the years of vaccination.

The weather has played a major role in several outbreaks of leptospirosis in the ROK [28]. Heavy rains or floods increase the spreading of infections, especially in areas with inhabitation of wild rodents, by washing leptospires out of the surface waters or by modifying human behaviors. There was a report of 12 Korean Combat Police and policemen contracting leptospirosis apparently from risk exposures to a wet environment following floods and typhoons in September 2000. All of them were barefooted while working in the rice fields of a flooded area. Some of them had abrasions on either the hands or the feet [43].

With global climate change, particularly increasing flooding and rising temperatures, there has been increasing concern regarding both an upsurge in disease incidence and the magnitude of leptospirosis outbreaks [50]. Statistical modeling using meteorological data has been studied recently to predict disease epidemics as well as to implement seasonal preventive measures. A study in southern Brazil reported that maximum daily and total monthly rainfalls for the present and previous months were statistically significant predictors of the number of cases of leptospirosis in Poisson regression models [51]. Another study using time series analysis identified a significant correlation between the number of cases in a given month and the associated cumulative rainfall as well as the mean monthly temperature recorded 2 months prior to diagnosis [52]. The study by Robertson et al. indicated a 2-month lag in rainfall-case association during the baseline period, but the role of rainfall in the outbreak revealed a more complex relationship [53]. Meanwhile, a recent Korean study did not show a positive correlation between precipitation and the incidence of leptospirosis [54].

Wild rodents, particularly *A. agrarius,* have been known as the major animal carrier associated with human infection in the ROK since 1984. These reservoirs carry mainly serovar *lai* [30]. However, there are only a few available studies on infection rates in wild small mammals in recent years. In a survey performed in the Yeonchon and Paju areas in 2001 and 2002, an infection rate of 5.56% was reported in captured *A. agrarius,* determined by detection of leptospiral DNA [56]. Two other studies performed in the military training places located near the demilitarized zone separating North and South Korea in 2001-2007 showed low seropositivity of leptospirosis (1.3%-1.5%) only in *A. agrarius,* but it is hard to compare the results with the previous studies because of the different places [57, 58]. On the other hand, a seroepidemiological study of selected rodent-borne diseases was conducted among rodents in an urban environment (Yongsan Garrison, Seoul) from 2001 through 2005, as part of the U.S. military rodent surveillance and control program. *Rattus norvegicus* accounted for nearly all of the rodents captured (99.8%) and were the only rodents that were serologically positive for SEO virus (9.6%), scrub typhus (2.8%), murine typhus (3.8%), and leptospirosis (4.6%) [59]. The clinical relevance of this seropositivity for leptospirosis remains to be clarified.

Recently, two Korean studies investigated the seroprevalence of leptospirosis among zoo animals and riding horses [60, 61]. Historically, isolation of *L. interrogans* from a dead skunk at Seoul Zoological Garden was described by Takagi before World War II [62]. There have been few seroprevalence studies conducted on zoo animals. In one study of 118 zoo animals, the prevalence of leptospiral antibodies was 25%, mostly reactive to serovar *sejro*e (87%) [60]. The other study, which examined 1,226 healthy racing horses, showed 25.0% seropositivity with reactivity to serovars *sejroe* (73.1%), *bratislava*, *ballum*, *autumnalis*, and *canicola,* in decreasing frequency [61]. Animal carriers may shed leptospires in the urine for many weeks or months after the acute phase or after an inapparent infection. Collectively, these findings suggest that serovar *sejroe* may be maintained within these animal populations. Therefore, further studies to isolate leptospiral strains or to detect leptospiral DNA by the polymerase chain reaction assay from these animals are needed, together with analysis of free-living rodents in the surrounding environment. In the meantime, consideration may be given to the inclusion of serovar *sejro*e in diagnostic tests for human leptospirosis in the ROK.

In spite of the relatively low prevalence of leptospirosis in recent years, the disease continues to be a threat to people in endemic areas. In a study of leptospirosis conducted in a tertiary care hospital in Jeonnam province in 2001-2007, Jung et al. retrospectively analyzed clinical severity by the presence of pulmonary involvement. The patients with pulmonary involvement (n=44) more frequently experienced dyspnea, hemoptysis, renal dysfunction, thrombocytopenia, and mixed organ involvement, compared to those without pulmonary involvement (n=22). Moreover, 80% of patients with pulmonary involvement had hemoptysis, and 31.8% of these patients required mechanical ventilatory support. All 4 fatal cases had pulmonary involvement with acute respiratory failure. The study concluded that close monitoring and intensive care are important for patients with pulmonary involvement [44]. Early diagnosis and prompt treatment may reduce clinical severity or the mortality from this disease. Therefore, socioeconomic factors such as access to health care or the availability of public health services in rural endemic areas should be taken into consideration for the improvement of clinical outcomes.

Conclusions

Leptospirosis is an important public health problem in the ROK. From the old findings, as long as wild rodent reservoirs persist, there is always high concern for potential outbreaks when floods or heavy rainfalls are expected around the harvest season. Furthermore, several new findings from the literature bring additional concerns regarding the potential spread of the disease in communities, requiring further investigation to define current changes in ecology, epidemiology, and the disease burden in both humans and animals in the ROK.

The author proposes several avenues of research focusing on the following issues: 1) Ecological research on identification of new potential animal reservoirs (domestic animals, livestock, etc.) and their clinical relevance in communities under the multidisciplinary science collaboration. 2) Epidemiological studies on predicting factors of sporadic infection or outbreaks in endemic areas, including climate change and various environmental risk factors. 3) Continuation of serosurveillance for patients with acute febrile illness in endemic areas. 4) Development of new rapid diagnostic tests that can be easily applicable to laboratory facilities.

Finally, the author recommends national policy regarding construction and maintenance of the weighted wildlife monitoring system and the enhanced disease surveillance program to facilitate better monitoring and understanding of this disease.

Conflicts of interest

No conflicts of interest.

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