NOTE
Public Health

Associations between Japanese spotted fever (JSF) cases and wildlife distribution on the Boso Peninsula, Central Japan (2006–2017)

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ABSTRACT. Populations of large mammals have been dramatically increasing in Japan, resulting in damage to agriculture, forestry, and ecosystems. However, their effects on tick-borne diseases have been poorly studied. Here, we focused on the relationship between Japanese spotted fever (JSF), a tick-borne disease caused by *Rickettsia japonica*, and populations of large mammals. To explore factors that affected the area in which JSF cases occur, we used generalized linear mixed models (GLMMs). We demonstrated that the expansion of the area of JSF occurrence can be predicted by deer density and geographical factors, which is likely due to differences in landscape structure. However, the associated models have limitations because of the lack of information about the distribution of vectors and reservoirs. To reduce the risk of humans contracting JSF, potential reservoirs should be confirmed.

KEY WORDS: Japanese spotted fever, Reeves's muntjac, sika deer, tick-borne disease, wild boar

Populations of large mammals have been dramatically increasing in Japan. These increases in mammalian populations have caused substantial damage to agriculture, forestry, and ecosystems [14, 34, 38]. However, their effects on tick-borne diseases or zoonotic diseases carried by hard ticks have been poorly studied in Japan [29]. In Europe and the US, relationships between large mammals and tick-borne diseases have been well documented, especially Lyme disease, the most frequently reported vector-borne disease, which is caused primarily by *Borrelia burgdorferi*. These studies have shown that large mammals, such as white-tailed deer (*Odocoileus virginianus*) and roe deer (*Capreolus capreolus*), support the feeding and reproduction of adult ticks [17, 42, 46]; however, it has also been shown that these deer are not necessarily reservoirs of Lyme disease. Such knowledge has contributed to the prevention of Lyme disease. To date, however, no such knowledge is available with regard to tick-borne diseases caused by other agents, including rickettsia.

In this study, we focused on the relationship between Japanese spotted fever (JSF), a tick-borne disease caused by *Rickettsia japonica*, and populations of large mammals. JSF was first described in Japan in 1984 [22]. The number and distribution of JSF cases have tended to increase and expand since then; more than 200 cases were reported in 2014, compared to approximately 50 cases each year from 1999 to 2002 [27, 47]. This trend has been suggested to be a result of the spread and expansion of wildlife populations and/or because the disease is more readily recognized by doctors [23]. For example, a previous study in Shimane Prefecture, Japan, showed that the number of JSF cases decreased after shrinkage of sika deer (*Cervus nippon*) population the Misen Mountains, where no other large mammals lived [39]. Although a rickettsia group closely related to *R. japonica* with the potential to cause JSF was detected in *Haemaphysalis longicornis* feeding on Japanese wild boar (*Sus scrofa leucomystax*) in Kyoto City [37], Japan, the effects of wild boar density on the area in which JSF cases occur have not been considered in previous studies.

This study was conducted on the Boso Peninsula of Chiba Prefecture, central Japan (35°N, 140°E), where the spatial distributions of deer, wild boar, and Reeves's muntjac (*Muntiacus reevesi*) have been studied for the past twelve years at a fine resolution (Fig. 1). In addition, JSF and scrub typhus (ST) are endemic to the southern Boso Peninsula [27]. *Ehrlichia,* which causes human ehrlichiosis, was detected in ticks in the area with polymerase chain reaction (PCR) [41]. In particular, the area in which JSF cases occur on the Boso Peninsula has been expanding since the first case was described in 1987 [18, 19, 26]. Using
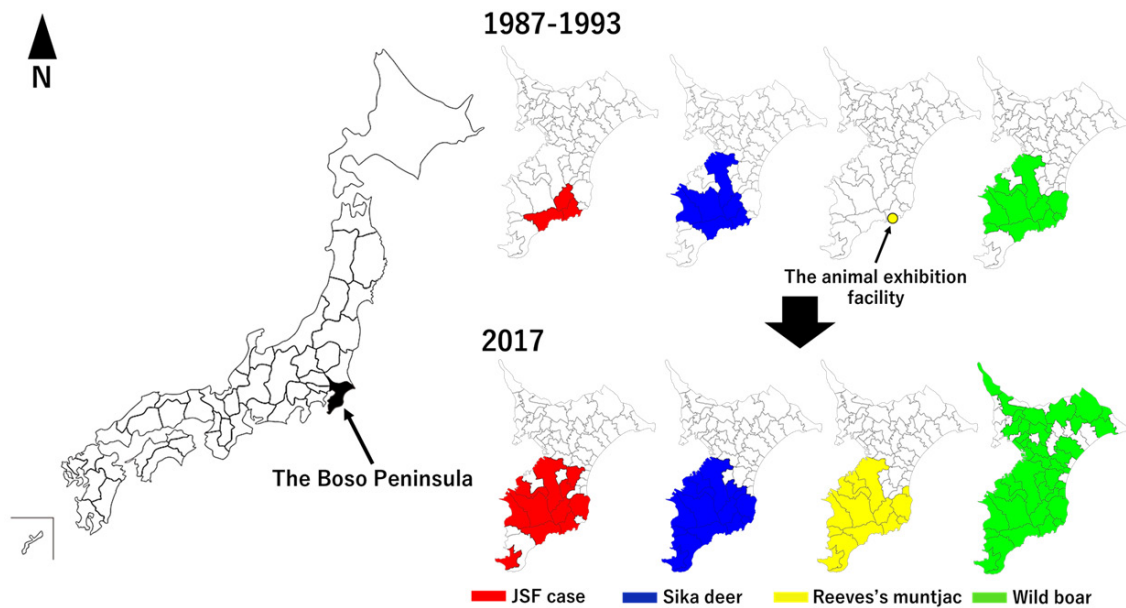
Fig. 1. Distributions of Japanese spotted fever (JSF) cases, sika deer, Reeves's muntjac and Japanese wild boar from 1987 to 2017 on the Boso Peninsula, Central Japan. The distribution of JSF cases is based on a previous report [26]. The sika deer and wild boar distributions from 1987-1993 are based on observational data [2, 5]. Reeves's muntjac, which is an invasive species in Japan, escaped from an animal exhibition facility between 1960 and 1980. However, the monitoring of Reeves's muntjac distribution started in 1998. In 2017, the sika deer, Reeves's muntjac and wild boar distributions were based on data provided by Chiba Prefecture and the Deer Research Group.

these data, we examined the effects of increases in the deer, wild boar, and Reeves's muntjac populations on JSF cases over a period of 12 years.

The Boso Peninsula is characterized by a warm temperate climate. The dominant vegetation of the peninsula is broad-leaved evergreen forest and coniferous plantations. Forest accounts for one-third of the area of Chiba Prefecture. According to the census, the total population was 840,000 in 2006 and 750,000 in 2017 [6]. From 2006 to 2017, an average of 5 JSF cases were reported each year [27].

Sika deer are native to the Boso Peninsula; the population of sika deer on the peninsula is isolated from other populations on the mainland. The distributional area of the deer population on the Boso peninsula was 40 km² in 1974 [7], but it had increased to 1,831 km² by 2015 [8]. Reeves's muntjac is an invasive species in Japan. In the case of the Boso Peninsula, it escaped from an animal exhibition facility between 1960 and 1980. Its population reached approximately 50,000 in 2015 [9]. On the Boso Peninsula, Japanese wild boar was artificially introduced in the mid-1980s after it had been extirpated in the mid-1970s [2]. Approximately 23,000 wild boars were captured in 2015 [10]. Wild boar is suspected to be an amplifying host for rickettsial disease caused by *Rickettsia tamurae* [13, 15, 25]. Although human *R. tamurae* infection has not been reported on the Boso Peninsula, *R. tamurae* DNA was detected by PCR in samples from *Amblyomma testudinarium* (Matsuyama: unpublished data).

Annual estimates of sika deer and Reeves's muntjac populations from 2006 through 2017 were provided by the government of Chiba Prefecture and the Deer Research Group in Boso (for further details on the method of determining the population density, see [34]). We estimated the population density of deer and muntjac per local municipality by dividing their populations by the area of the municipality (per square kilometer). Annual hunting reports of wild boar captured by traps in each municipality from 2006 through 2017 were provided by the government of Chiba Prefecture and the Deer Research Group in Boso. We indexed the annual density of wild boars as the number of wild boars captured in that region divided by the area of the municipality (number of boars per square kilometer).

Records of JSF cases reported each year in each municipality from 2006 through 2017 were provided by the Chiba Prefectural Institute of Public Health.

We selected 14 local municipalities in and around the area in which JSF cases have ever been reported (Fig. 1). The first JSF case in this region was reported in Amatsu-Kominato town of Kamogawa city in 1987 [19]. The differences in latitude and longitude (degree) between the city halls of each municipality and those of Amatsu-Kominato town (Currently Amatsu-Kominato branch of Kamogawa city hall) were calculated, and they represent the differences in the absolute values of the latitude (ALA) and longitude (ALO), respectively. To explore the factors that affected JSF cases, we used generalized linear mixed models (GLMMs) with the package glmmADMB [12] in R ver. 4.0.0. [33]. We used the number of JSF cases in each municipality as the response variable (assuming a zero-inflated Poisson distribution via a log-link function) and set the following factors as explanatory variables: deer density, muntjac density, index of wild boar density (wild boar density), year, ALA, ALO, the squared ALA and the squared ALO. The parameters ALA and ALO were included to test the effects of the distance and direction from the location of the

first JSF case report.

Unknown differences among municipalities was added to the model as a random factor. We initially selected the most parsimonious model by backward selection from the full model, added each parameter back to the model, and then determined whether the model was improved to avoid choosing a local best model. Models were compared based on the Akaike Information Criterion (AIC). The significance of the explanatory parameters in the best model was determined with the Wald test.

JSF cases were significantly affected by deer density and geographical factors, based on the fact that the best model included deer density, ALO and squared ALA (Tables 1 and 2). The impact of deer density was clear, and the best model had a smaller AIC than the 2-parameter model that included ALO and ALA (254.1). On the Boso Peninsula, sika deer may serve as hosts of *Haemaphysalis* ticks that are suspected JSF vectors, such as *H. longicornis*, *H. flava*, *H. megaspinosa*, and *H. cornigera* [31, 40, 45]. Compared with other rickettsial genotypes in Japan [43], *R. japonica* shows a wide association with many tick species [1] that preferentially parasitize deer. The presence of deer is unlikely to affect the infection prevalence of *R. japonica* in ticks, although it might increase the density of infected ticks. For example, a positive associated has been reported between the abundance of *H. longicornis* and *H. megaspinosa* and deer density [*e.g.* 24, 44]. Expansion of the deer population might have led to an increased abundance and an expanded distribution of these ticks, resulting in an increased human risk of contracting JSF. However, it remains unclear whether deer are reservoirs of JSF. Only one report is available on the existence of *Rickettsia* in the peripheral blood of sika deer; in that study, *Rickettsia helvetica*, not *R. japonica*, was detected [16].

The geographic distribution of JSF does not seem to be determined solely by the distribution of reservoirs. The best model included ALO and squared ALA (Table 2). The positive association of ALO with JSF cases might be explained by the large forest belt expanding from the region in which the first JSF case occurred in an east-west direction (Fig. 2), providing a path for the expansion of the populations of large mammals, which serve as the final hosts of the tick [11]. On the other hand, squared ALA was negatively associated with JSF cases, possibly because in the north-south direction from the region in which the first JSF case occurred lies a suburb of Kamogawa city, and those directions are largely occupied by urban spaces, which can be an obstacle to the expansion of the deer population. This speculation is supported by a previous study in which the dispersal of the deer population in Boso was estimated to have expanded along with the continuity of the forests [30]. By incorporating deer density and the geographic factors that were used by this study into the distribution model of infected ticks, we may further predict the human risk of contracting JSF.

The density of Reeves's muntjac was not selected in the best model but was slightly associated with JSF cases in the full model. Considering the greater speed of range expansion of Reeves's muntjac than that of deer [4, 5], the effect of the expansion of the range of Reeves's muntjac might have appeared years later. To test this possibility, we included the muntjac density of the prior year instead of the present year's density as an explanatory variable in the GLMMs; however, this change did not affect the result. Nevertheless, Reeves's muntjac is a potential reservoir for JSF in this region, as suggested by the fact that its distribution overlaps with the area in which JSF cases occur [36].

Table 1. Results of model selection of Japanese spotted fever (JSF) cases

Rank	Variable[a]	AIC	ΔAIC
The number of Japanese spotted fever cases=			
Full model 1	Deer density*** + Muntjac density + Wild boar density + Year + ALA* + ALO + Municipality	199.0	0.0
Full model 2	Deer density*** + Muntjac density + Wild boar density + Year + ALA^2 * + ALO + Municipality	198.0	1.0
Model 1	Deer density*** + Muntjac density + Wild boar density + ALA^2 * + ALO + Municipality	197.5	1.5
Model 2	Deer density*** + Wild boar density + ALA2 ** + ALO + Municipality	195.5	3.5
Model 3	Deer density*** + ALA^2 ** + ALO + Municipality	193.5	5.5
Model 4	Deer density*** + ALA^2 ** + Municipality	194.4	4.6
Model 5	Deer density*** + ALA^2 **	192.4	6.6
Best model	Deer density*** + ALA^2 ** + ALO	191.5	7.5

a) Variables refer to ALA: the differences in the absolute values of the latitude of each city hall and that of Amatsu-Kominato town; ALO: the differences in the absolute values of the longitude of each city hall and that of Amatsu-Kominato town. Aasterisks: significantly different from 0 in Wald test (*P<0.05; **P<0.01; ***P<0.001). AIC, Akaike Information Criterion.

Table 2. Results of the best model in Table 1

Variable[a]	Estimates	SE	z value	Confidence interval	
				2.5%	97.5%
Intercept	−3.11	0.51	−6.13	−4.10	−2.11
Deer density	0.14	0.02	7.42	0.11	0.18
ALA^2	−14.31	4.38	−3.27	−22.90	−5.73
ALO	2.33	1.38	1.68	−0.38	5.04

a) Variables refer to ALA: the differences in the absolute values of the latitude of each city hall and that of Amatsu-Kominato town; ALO: the differences in the absolute values of the longitude of each city hall and that of Amatsu-Kominato town.
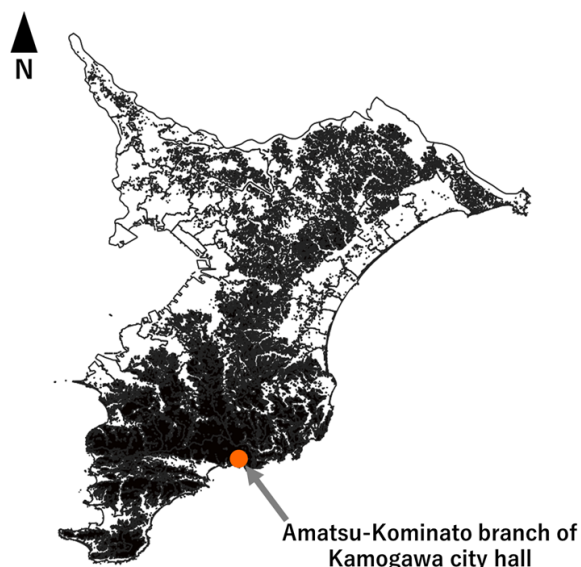
Fig. 2. Forest area on the Boso Peninsula in 2015. The figure was produced using QGIS [32]. The polygon data for the forest area were from the National Land Information Division [28]. Black areas indicate the forest areas. White areas mainly represent residential areas.

The density of wild boar was not selected in the best model, although its density was slightly associated with JSF cases in the full model. On the northern Boso Peninsula, where there are neither deer nor Reeves's muntjac [4, 5], there are wild boar [3, 10]; however, no cases of JSF have been reported [26] (Fig. 1). Based on the results of the full and best models and the association between the distribution of wild boar and the area in which JSF cases occur, wild boar is not expected to be the reservoir for JSF in this region. However, the density of captured wild boar might have been a poor indicator of the true population density of wild boar. Thus, obtaining an accurate estimation of wild boar density is a challenging but necessary task for further assessment of this issue.

We demonstrated that the expansion of the area in which JSF cases occur can be predicted by deer density and geographical factors, likely due to differences in landscape structure. However, the associated models have limitations because of the lack of information about the distribution of vectors and reservoirs. To understand the dynamics of JSF and to reduce the human risk of contracting JSF, potential reservoirs of rickettsial agents in the wild, including vertebrates, questing ticks and land leeches (*Haemadipsa zeylanica japonica*) [20, 21, 35], should be confirmed. At the same time, we need to also investigate more details about the effects of ecological factors on host-vector-pathogen systems.

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