Final Report

Project Title Lattice-based Model for leptospirosis endemic including the role of seasonal effect in Thailand

By Sudarat Chadsuthi

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Abstract

Project Code : MRG61800051

Project Title : Lattice-based Model for leptospirosis endemic including the role of seasonal effect in Thailand

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Abstract:

The epidemic of leptospirosis in animals and humans continues to this day, causing incidences annually in Thailand. The infection of humans and animals is mainly caused by direct contact with infected animals and also by indirect contact with urine of infected animals through cuts in the skin or mucous membranes in a contaminated environment. In case of flooding, leptospires could be spread into environment, increasing the risk of leptospirosis infection. The aim of this study was (1) to investigate the association of several environmental factors with cattle and buffalo leptospirosis cases in Thailand, focusing on the role of flooding, (2) to propose different leptospirosis transmission models for humans, which considers the impact of environmental factors such as seasonal flooding, and weather conditions, and (3) to use a spatial model as a stochastic cellular automata model for studying the impact of (the modified normalized difference water index) MNDWI and rainfall on the transmission of leptospirosis in Si Sa Ket, Thailand. We found that the percentage of flood area and MNDWI are significant factors for leptospirosis infection in cattle and buffalo, and humans. We found that the model with the transmission rate dependent on flooding or MNDWI is the most important for leptospirosis in Thailand, indicating a high degree of flooding leads to higher cases. Sensitivity analysis showed that the transmission of leptospires from the contaminated environment was the most important parameter for the total number of human cases. Our results suggest that public health policy makers should guide the people who work close to, or in contaminated environments to avoiding potential sources of leptospirosis, or by protecting themselves by wearing boots to reduce the leptospirosis outbreak.

Keywords : Leptospirosis, Animals, Humans, Flood, Contaminated environment

1. Abstract

The epidemic of leptospirosis in animals and humans continues to this day, causing incidences annually in Thailand. The infection of humans and animals is mainly caused by direct contact with infected animals and also by indirect contact with urine of infected animals through cuts in the skin or mucous membranes in a contaminated environment. In case of flooding, leptospires could be spread into environment, increasing the risk of leptospirosis infection. The aim of this study was (1) to investigate the association of several environmental factors with cattle and buffalo leptospirosis cases in Thailand, focusing on the role of flooding, (2) to propose different leptospirosis transmission models for humans, which considers the impact of environmental factors such as seasonal flooding, and weather conditions, and (3) to use a spatial model as a stochastic cellular automata model for studying the impact of (the modified normalized difference water index) MNDWI and rainfall on the transmission of leptospirosis in Si Sa Ket, Thailand. We found that the percentage of flood area and MNDWI are significant factors for leptospirosis infection in cattle and buffalo, and humans. We found that the model with the transmission rate dependent on flooding or MNDWI is the most important for leptospirosis in Thailand, indicating a high degree of flooding leads to higher cases. Sensitivity analysis showed that the transmission of leptospires from the contaminated environment was the most important parameter for the total number of human cases. Our results suggest that public health policy makers should guide the people who work close to, or in contaminated environments to avoiding potential sources of leptospirosis, or by protecting themselves by wearing boots to reduce the leptospirosis outbreak.

โรคเลปโตสไปโรซีสเป็นโรคที่ระบาดทั้งในคนและสัตว์ในประเทศไทยต่อเนื่องจนถึงปัจจุบัน การติดเชื้อในคนและสัตว์เกิดจากการไปสัมผัสกับสัตว์ที่เป็นโรคโดยตรง หรือไปสัมผัสกับสิ่งแวดล้อมที่ปนเปื้อนเชื้อโรคนี้อยู่ แบคทีเรียเลปโตสไปราสามารถอยู่ในสิ่งแวดล้อมได้เมื่อมีน้ำท่วมขังซึ่งเป็นสาเหตุของการติดเชื้อ งานวิจัยนี้มีวัตถุประสงค์คือ (1) เพื่อศึกษาความสัมพันธ์ของปัจจัยทางสิ่งแวดล้อมโดยเฉพาะปัจจัยน้ำท่วมกับการเกิดโรคในวัวและควาย (2) เพื่อสร้างสมการทางคณิตศาสตร์สำหรับการส่งผ่านโรคในคนโดยคำนึงถึงปัจจัยน้ำฝน น้ำท่วม และอุณหภูมิ และ (3) เพื่อสร้างแบบจำลองเชิงพื้นที่ (stochastic cellular automata model) สำหรับกรระบาดของโรคในคน โดยใช้ดัชนีน้ำท่วม และน้ำฝนเป็นตัวแปรที่ขึ้นกันความน่าจะเป็นในการส่งผ่านโรค จากการศึกษาพบว่า ปัจจัยน้ำท่วมและดัชนีน้ำท่วม เป็นตัวแปรที่สำคัญในกรเกิดโรคของวัว ควาย และคน จากการเปรียบเทียบแบบจำลองต่าง ๆ ยังพบอีกว่าความน่าจะเป็นในการส่งผ่านโรคในคนจะขึ้นกับปัจจัยน้ำท่วมเป็นหลัก หมายความว่าน้ำท่วมจะทำให้จำนวนผู้ป่วยสูงขึ้น ซึ่งเกิดจากการส่งผ่านโรคจากสิ่งแวดล้อมมาสู่คนเป็นหลัก ผลของการศึกษาสามารถนำมาเป็นข้อมูลประกอบการตัดสินใจในการหามาตรการเพื่อควบคุมการระบาดเมื่อเกิดน้ำท่วม อีกทั้งยังสามารถนำมาเป็นข้อมูลพื้นในการรณรงค์ให้ผู้ที่ทำงานใกล้ชิดกับสิ่งแวดล้อมป้องกันตนเองโดยการสวมร้องเท้าก่อนลงสู่แหล่งน้ำ

2. Executive summary

Leptospirosis is a worldwide zoonotic bacterial disease, that is particularly endemic in tropical and subtropical countries. The infection of humans and animals is mainly caused by direct contact with infected animals and also by indirect contact with urine of infected animals through cuts in the skin or mucous membranes in a contaminated environment. In this work, we first investigated the association of several environmental factors (especially remotely sensed indicators of flooding) with cattle and buffalo leptospirosis cases in Thailand. We then developed a mathematical model to study the transmission dynamics between humans, animals, and a contaminated environment in Si Sa Ket. We compared different models that included the impact of flooding and weather conditions on the transmission rate from a contaminated environment, the leptospire shedding rate and the multiplication rate of the leptospires in the environment. We found that the model with the transmission rate dependent on flooding and temperature best-fit the reported human data on leptospirosis in Thailand. Finally, we study the impact of (the modified normalized difference water index) MNDWI on the transmission of leptospirosis using a stochastic cellular automata model in Si Sa Ket, Thailand, which has the highest reported cases from 2014 to 2018. This study highlighted that seasonal MNDWI contributed to the transmission dynamics of leptospirosis. We also investigated the epidemic size, which is the sum of overtime cases, was investigated to find the critical transmission probability from endemic to epidemic state.

For leptospirosis in animals, our findings could identify flooding as a major driver of the risk of leptospirosis infection in cattle and buffalo. When flooding or heavy rainfall occurs, the water picks up contaminated soil and animal excreta from the soil. This results in the spread of leptospirosis through contaminated water. Flooding could possibly be the principal reason for leptospirosis epidemics above other factors.Flood control could be an option to reduce the risk of leptospirosis infection in animals, which can be a major reservoir for human infection.

For leptospirosis in humans, our results highlight that flooding indicators have the most impact on transmission, indicating a high degree of flooding leads to higher cases. Sensitivity analysis showed that the transmission of leptospires from the contaminated environment was the most important parameter for the total number of human cases. The results of SCA model predicts the significant environment factor associated with leptospirosis transmission is flooding.

Our model allows to identify areas and periods when the risk of leptospirosis infection is higher in cattle and buffalo, mainly due to a seasonal flooding. These areas and periods should be targeted for leptospirosis surveillance and control in both humans and animals. Our results also suggest that public health policy makers should guide the people who work close to, or in contaminated environments to avoiding potential sources of leptospirosis, or by protecting themselves by wearing boots to reduce the leptospirosis outbreak. Public awareness about the risk of leptospirosis during flooding should be raised in order for people to take prevention measures when possible.

3. Objective

1. To investigate the association of several environmental factors (especially remotely sensed indicators of flooding) with cattle and buffalo leptospirosis cases in Thailand.
2. To use the environmental factors (flooding indicator, the amount of rainfall and temperature) for investigating the disease spread of leptospirosis in animals and humans in Thailand based on the SIR leptospirosis transmission model in Si Sa Ket province. The model that fit to the incidence data is used to study the control strategies.
3. To develop the lattice-based leptospirosis transmission model in Si Sa Ket province and characterize some statistical mechanic properties such as phase transition between an absorbing state and an active state.

4. Research methodology

4.1 Data

Epidemiological Data

The animal data of a total of 3,571 urine samples derived from 488 buffalo and 3,083 cattle, were collected from January 2011 to February 2013 under a cross-sectional program, which has been described in detail in a recent article [1]. All urine samples were examined for the presence/absence of leptospiral infection by loop-mediated isothermal amplification (LAMP) method [1, 2]. This technique showed high sensitivity and specificity at 96.8% and 97.0%, respectively [2].

The reported cases of human leptospirosis were retrieved from the national disease surveillance (report 506), Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand [3]. Most positive cases were suspected leptospirosis cases, based on the clinical diagnosis made by attending physicians. The clinical criteria for leptospirosis were high fever, chills, headache, with at least one of the following symptoms including abdominal pain, red eyes, neurological symptoms (such as stiffness, abnormal feelings, etc.), and dry cough or cough with bloody sputum, and a career history of exposure to water areas or environments contaminated with animal excreta [4]. Some of the suspected cases were then examined using laboratory tests such as Latex agglutination test (LA), Dipstick test, Lateral flow test, Microcapsule agglutination test (MCAT), Immunofluorescent antibody test (IFA), Microscopic agglutination test (MAT) or ELISA for confirmation. The suspected cases were mainly reported from public hospitals with a small fraction from private hospitals. In this research, we analyzed all reported cases from 2010 to 2016 in two provinces (*i.e.*, Si Sa Ket and Surin), in which the highest number of cases were reported.

Human data collection was performed as a part of routine clinical examination procedures of the Thai Ministry of Public Health surveillance and response. Data collection was approved by the Ethics Committee of the Ministry of Public Health of Thailand. Data containing the patient's medical records, without any patient information except location, were de-identified prior to analysis.

Environmental data

The amount of rainfall was obtained from near Real-time TRMM (Tropical Rainfall Measuring Mission) multi-satellite precipitation analysis (TMPA-RT), which is produced at the National Aeronautics and Space Administration, Goddard Earth Sciences Data and Information Services Center (NASA GES DISC) [5]. The daily accumulated precipitation product is generated from the Near Real-Time Precipitation 3-hourly 1 day TMPA at a spatial resolution of 0.25 degree x 0.25 degree Version 7 (TRMM 3B42RT Daily) [6, 7]. In this study, given the homogeneity of rainfall at the district level, we only extracted the TRMM data at the centroid of each district.

To identify flooded areas, we used the data from the Moderate Resolution Imaging Spectroradiometer (MODIS) of the Terra satellite (Surface Reflectance 8-Day L3 Global 500m SIN Grid V005 (MOD09A1)). In each image pixel, the data provides an estimation of the surface spectral reflectance measured at ground level in the absence of atmospheric scattering or absorption. The band 4 (green) and band 7 (infrared) were used to calculate the modified normalized difference water index (MNDWI) [8, 9], which allows an estimate of the water presence in each pixel. Within all districts, each pixel was classified as flooded if the MNDWI value was more than or equal to zero. This threshold of zero for MNDWI is in the range of optimal thresholds calibrated in previous studies [8, 10, 11]. Permanent water bodies such as rivers and lakes were masked out using QGIS version 2.8.3 [12]. Then, the number of flooded pixels were counted to calculate the percentage of flooded land in each district.

The LST was extracted from the MODIS Terra product (MOD11A2) with Emissivity 8-Day L3 Global 1 km, which is composed of the daily LST product (MOD11A1) with a 1 km resolution and stored on a 1 km Sinusoidal grid as the average values of clear-sky LSTs during an 8-day period[13].

Elevation can be associated with slopes and increased movement of surface water [14], but slope data was not available at a national scale in Thailand. Elevation data was derived from the NASA Shuttle Radar Topographic Mission (SRTM) 90m Digital Elevation Data, which provides elevation data for the entire world (http://srtm.csi.cgiar.org/index.asp). The average elevation at the district level was used in the model.

Human population data was obtained from the WorldPop database, which presents the number of people per hectare (http://www.worldpop.org.uk). Human population density was included in the model because it could be associated with different agricultural practices in areas with different levels of economic development. The animal population density of livestock species (buffalo, cattle, goat, pigs and sheep) were obtained from the Information and Communication Technology Center (ICT), Department of Livestock Development of Thailand at the district level (http://ict.dld.go.th). Goats, pigs and sheep were included because they may also contribute to the circulation of leptospirosis in cattle and buffaloes. Seroprevalences of other livestock were shown in Thailand from January to August 2001 in a previous study [15]. In this study, no urine samples were collected in urban districts because limited number of cattle and buffaloes are found in areas of high human population density. The districts with a human population density above 1400 people/km^2, which corresponds to the urban centers of the main cities of Thailand, and no livestock were not included in the risk mapping given the limited number of animals in urban centers.

4.2 Model

Statistical model

To investigate the association between of several environmental factors (especially remotely sensed indicators of flooding) and leptospirosis infection in animals, we first study univariate linear regressions. Using a generalized linear mixed model (GLMM) with a logit link since the response variable had a binomial distribution. We used R software [16] with the package lme4 [17]. Since all individual urine samples were not independent because they were collected during common sampling occasions, we used the sampling occasion index as a random effect variable. Each sampling occasion was identified by a date, a year and a district geocode. The best multivariable model was selected using a stepwise backward approach based on the Akaike Information Criterion (AIC). The Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC) plot was used to estimate the model performance. We also used cross-validation to measure the performance of the best model. Data was randomly split into training (2/3 of data) and test (1/3 of data) sets. Training data is used to produce the prediction model, while the test data is used to test the model performance. Given the size of our dataset, we chose to keep 2/3 of the data in the training set to optimize model performance. We performed repeated cross-validations 1,000 times to estimate the mean and standard deviation of the cross-validated AUC (cvAUC) of the best model.

The best model was used to predict leptospirosis infection risk in 2012 and 2016 for three periods (mid-January, mid-May and mid-September) which represents the middle of the dry season, the beginning of the rainy season and the end of the rainy season, respectively for central and northern Thailand.

Mathematical model

To use the environmental factors (flooding indicator, the amount of rainfall and temperature) for investigating the disease spread of leptospirosis in animals and humans in Thailand, we developed a simple SIR model. Susceptible human and livestock individuals are introduced, denoted by S_h and S_a, respectively. S_h and S_a can become infected through contact with infected livestock and/or the contaminated environment. The infected livestock can shed leptospires into the environment and increase the number of leptospires (L compartment) in that province. The hygienic level of the contaminated environment can be defined as the density of leptospires. The leptospires die at a rate μ_L. Infected humans and animals recover at the constant rates γ_h and γ_a, and loss immunity at the rates ν_h and ν_a, respectively. Both population sizes are assumed to be constant. In this work, we developed the transmission model based on previous studies[18, 19]. The leptospirosis transmission model is described by the following set of differential equations:

$$\begin{aligned}
\frac{dS_h(t)}{dt} &= \mu_h N_h - \beta_{ha}(t)\frac{S_h(t)I_a(t)}{N_h} - \beta_{hL}(t)h(t)\frac{S_h(t)}{N_h} + \nu_h R_h(t) - \mu_h S_h(t),\\
\frac{dI_h(t)}{dt} &= \beta_{ha}(t)\frac{S_h(t)I_a(t)}{N_h} + \beta_{hL}(t)h(t)\frac{S_h(t)}{N_h} - \gamma_h I_h(t) - \mu_h I_h(t),\\
\frac{dR_h(t)}{dt} &= \gamma_h I_h(t) - \nu_h R_h(t) - \mu_h R_h(t),\\
\frac{dS_a(t)}{dt} &= \mu_a N_a - \beta_{aa}(t)\frac{S_a(t)I_a(t)}{N_a(t)} - \beta_{aL}(t)h(t)\frac{S_a(t)}{N_a(t)} + \nu_a R_a(t) - \mu_a S_a(t),\\
\frac{dI_a(t)}{dt} &= \beta_{aa}(t)\frac{S_a(t)I_a(t)}{N_a(t)} + \beta_{aL}(t)h(t)\frac{S_a(t)}{N_a(t)} - \gamma_a I_a(t) - \mu_a I_a(t),\\
\frac{dR_a(t)}{dt} &= \gamma_a I_a(t) - \nu_a R_a(t) - \mu_a R_a(t),\\
\frac{dL(t)}{dt} &= \omega(t)I_a(t) + m(t)g(t)L(t) - \mu_L L(t),
\end{aligned} \tag{1}$$

where $N = S + I + R$ for livestock and human compartments.

In this model, we assumed that, as a zoonosis disease, the human-human transmission does not exist[20]; thus infection in humans always developed from animal sources or the contaminated environment. The leptospires shedding from humans into the environment is neglected in our study as the likelihood is very low. The function $g(t) = \frac{\chi - L(t)}{\chi}$ in equation (1) represents the logistic growth multiplier, which allows the growth to depend on the current number of leptospires and limits excessive growth, where χ is the maximum carrying capacity, or saturating population size. A saturation term, $h(t) = \frac{L(t)}{L(t)+\kappa}$, is added to limit the effect of transmission due to the large number of leptospires [21, 22], where κ is the density of leptospires in the environment at which the transmission rate is $0.5\beta_L(t)$. The diagram of the model and its relationship between the compartments is provided in figure 1. A set of parameters is shown in Table 1.

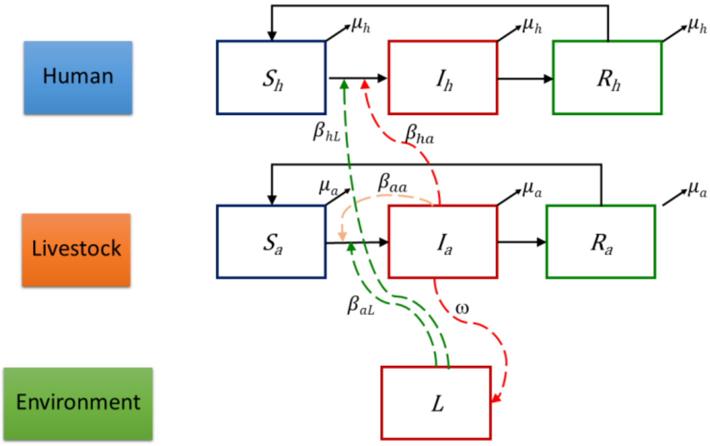

Figure 1. Dynamics of leptospirosis spread between humans, livestock and the contaminated environment. Dashed green arrow shows the transmission route from the contaminated environment to susceptible livestock (S_a) and humans (S_h). Infected livestock (I_h) transmit leptospires to humans and shed to environment (red dashed line) and to livestock (orange dashed line).

Table 1. A set of parameters.

Description	Symbol	Values
Birth and death rate of humans	$1/\mu^h$	70 years (estimated)
Duration of infection for humans	$1/\gamma^h$	14 days (estimated from [23])
Duration of loss of immunity for humans	$1/\nu^h$	720 days (estimated from [23])
Transmission rate from infected livestock to human	β_{ha}	fitted
Birth and death rate of livestock	$1/\mu^a$	3 years (estimated)
Duration of infection for livestock	$1/\gamma^a$	200 days (estimated from [24])
Duration of loss of immunity for livestock	$1/\nu^a$	540 days (estimated)
Transmission rate from infected livestock to livestock	β_{aa}	fitted
Duration of contamination for the environment	μ_L	0.02381 day^{-1} (estimated from [22])
Density of leptospires at which the transmission rate from the environment is 0.5$\boldsymbol{\beta_L(t)}$	κ	10^2 km^{-2} (estimated from [22])
Maximum carrying capacity	χ	1x10^5 (estimated)
Density of the free living leptospires in a province at $\boldsymbol{t=0}$	$L_i(0)$	10^{-3} km^{-2} (estimated from [22])
Density of leptospires shed per infected livestock	ω	fitted
Transmission rate from the contaminated environment to human and livestock	β_{hL} and β_{aL}	fitted
Multiplication rate of the leptospires in the environment	m	fitted

Some of the parameters in equation (1) may be affected by flooding and weather conditions. In this work, we look at how these conditions can affect the transmission from the contaminated environment, leptospire shedding rate, and the multiplication rate.

The most important parameters are the transmission modes from the contaminated environment to susceptible humans and susceptible livestock (β_{hL} and β_{aL}). We hypothesized that the environment could influence the transmission of leptospirosis. Thus, the transmission terms are constructed as a linear function of normalized data of the percentage of flooded area ($f(t)$), total monthly rainfall ($\rho(t)$), and average monthly temperature ($T(t)$). The virulence of leptospires depends on temperature [25], leading to the inclusion of the average temperature, which may impact the transmission model. We examined four forms of transmission rate dependency corresponding to three environmental variables to test different hypotheses. These four transmission rates assumed the rates were linearly proportional to the environmental variable and are as follows:

(1) Flooding (M1-F): The transmission rates are given by:

$$\beta_{hL}(t) = h_1\big(1 + h_2 f(t-\tau_1)\big)$$
$$\beta_{aL}(t) = a_2\big(1 + a_2 f(t-\tau_1)\big)$$

(2) Rainfall (M1-R): The transmission rates are given by:

$$\beta_{hL}(t) = h_1\big(1 + h_2 \rho(t-\tau_1)\big)$$
$$\beta_{aL}(t) = a_1\big(1 + a_2 \rho(t-\tau_1)\big)$$

(3) Flooding and temperature (M1-FT): The transmission rates are given by:

$$\beta_{hL}(t) = h_1(1 + h_2 f(t-\tau_1) + h_3 T(t-\tau_2))$$
$$\beta_{aL}(t) = a_1(1 + a_2 f(t-\tau_1) + a_3 T(t-\tau_2))$$

(4) Rainfall and temperature (M1-RT): The transmission rates are given by:

$$\beta_{hL}(t) = h_1(1 + h_2 \rho(t-\tau_1) + h_3 T(t-\tau_2))$$
$$\beta_{aL}(t) = a_1(1 + a_2 \rho(t-\tau_1) + a_3 T(t-\tau_2))$$

where h_i and a_i are constant values (that were fitted) of each function for each transmission rate, and τ_1 and τ_2 are time lags, varying from 0-8 weeks, which are associated with the infection of humans.

The second model (M2-F and M2-R) are the leptospire shedding rate (ω), which is affected by rainfall. Infected livestock shed leptospires into the environment, which will then be a source of exposure for susceptible humans and livestock. The shedding rate can be described as a logistic curve, to limit its effect at high concentrations.

$$\omega(t) = \omega_0\left(\frac{\rho(t-\tau_1)}{\delta+\rho(t-\tau_1)}\right) \text{ and } \omega(t) = \omega_0\left(\frac{f(t-\tau_1)}{\delta+f(t-\tau_1)}\right)$$

where δ is an inferred threshold parameter corresponding to the rate of half of the maximum shedding rate due to rainfall or the effect of flooding.

The last model affects the multiplication rate of the leptospires in the environment (m), which depends on three environmental variables, namely, the percentage of flooding area ($f(t)$), total monthly rainfall ($\rho(t)$) and average monthly temperature ($T(t)$). The multiplication rate is given by:

(1) Flooding (M3-F): $m(t) = x_1(1 + x_2 f(t-\tau_1))$

(2) Rainfall (M3-R): $m(t) = x_1(1 + x_2 \rho(t-\tau_1))$

(3) Flooding and temperature (M3-FT): $m(t) = x_1(1 + x_2 f(t-\tau_1) + x_3 T(t-\tau_2))$

(4) Rainfall and temperature (M3-RT): $m(t) = x_1(1 + x_2 \rho(t-\tau_1) + x_3 T(t-\tau_2))$

where x_1, x_2 and x_3 are constant values (fitted parameters).

Ten models (M1-F, M1-R, M1-FT, M1-RT, M2-F, M2-R, M3-F, M3-R, M3-FT and M3-RT) were considered individually and compared to the null hypothesis, where all parameters are constant values. The effect of flooding was compared to the effect of rainfall without and with a temperature effect. The combined models that use multiple effects above were also considered. A stochastic simulation approach was employed using a tau-leaping algorithm with a fixed time step [26]. Using the parameters of the best model, 1,000 simulations were generated.

Parameter estimation and sensitivity analysis for mathematical model

To estimate the parameters of mathematical model, we assumed that the epidemic was initiated by free-living leptospires in that area by setting the initial number of free-living leptospires to a low concentration (Table 1). We linked the biweekly human cases from the simulation results with the corresponding actual reported human cases from 2010 to 2015. The best fit was obtained by maximizing a normal log-likelihood estimation, which produced simulation results that were most similar to the reported data. We used the nlminb function in R, which is a quasi-Newton method with a constrained bound, to find the optimal set of parameters [27]. The model that shows the minimum negative log-likelihood was selected as the best model.

In this work, according to previous findings, we considered the effect of time lag (τ) on the environmental data to leptospirosis cases due to transmission. Rainfall has been observed to be associated with leptospirosis, often with a time lag of 1-3 months [28, 29]. We set the maximum time lags of flooding and rainfall to be eight weeks. We set the lag period to be the same for the effects of temperature, raining, and flooding in this model [30].

To perform a sensitivity analysis of which parameters influence the effect of leptospirosis transmission the most, we used the Partial Rank Correlation Coefficients (PRCC) technique [31, 32]. Then, we used the Latin hypercube sampling (LHS), which is a statistical Monte Carlo sampling technique, to sample the parameters using the lhs package in R [33]. 1,000 parameter sets were sampled with each parameter sampled from a uniform distribution. The PRCC was ranked as a response function to the cumulative new cases in each province using the sensitivity package in R with bootstrapping 1,000 times to obtain a 95% confidence intervals [34]. Based on the linear assumption, positive (negative) PRCC values imply positive (negative) correlations to the response function.

Estimation of time-dependent reproduction number (R_{td})

The basic reproductive number (R_0) is generally defined as the average number of secondary infected individuals caused by an infected individual in a population that is completely susceptible. Due to the complexity of the model and the time-dependent variables, there is no exact way to explain R_0 for this model, as it is a complex function of many different variables. An alternative method, proposed by Wallinga *et al* [35], computes the reproduction number from the observed cases using a likelihood-based method, calculated by averaging the overall transmission networks which makes it fit an epidemic curve [36]. In this work, we calculated a time-dependent reproduction number (R_{td}) according to the R0 package in R [36]. The number of biweekly cases obtained from the simulations of the best model in three provinces was used to estimate R_{td}. The serial interval between successive infections of the reported epidemic was identified and used to estimate the generation time distribution, with the mean and standard deviation (sd) of each province, using the R0 package. Then the R_{td} of each province was estimated with the 95% confidence interval.

Stochastic Cellular Automata model

To develop the lattice-based model for leptospirosis transmission in Si Sa Ket province, we proposed a Stochastic Cellular Automata (SCA) model, which is constructed based on the existing knowledge about leptospirosis transmission. There are two bi-dimensional square lattice size (1000×1000) where a cell is in position (i,j). The total population is assumed to be 350,000 individuals, who have agricultural and farmer worker at Si Sa Ket. Each individual (H_{ij}) is chosen randomly on a cell. Thus, human lattice will consist of occupation site or empty site. Human individual can assume to be one of four states, which is in a susceptible state (S), an exposed state (E), an infectious state (I), and a recovered state (R) as illustrated in figure 2.

The environment lattice can contain both empty sites and contaminated environment site (representing the source of leptospirosis if infected), which estimated to 60% of lattice size (figure 2). To simplify the model, we assumed that contaminated environment cell can transmit the infection to humans when there are in the same site. In this model, we used the periodic boundary condition and take each time step to correspond to one day. In each cell (H_{ij}), human occupation is chosen randomly. Usually, the human mortality rate approximates 1/70 years, which is small compared to the simulation time. Hence, we do not account for significant deaths. We assume that the death rate of leptospirosis is zero as it is a small number [37].

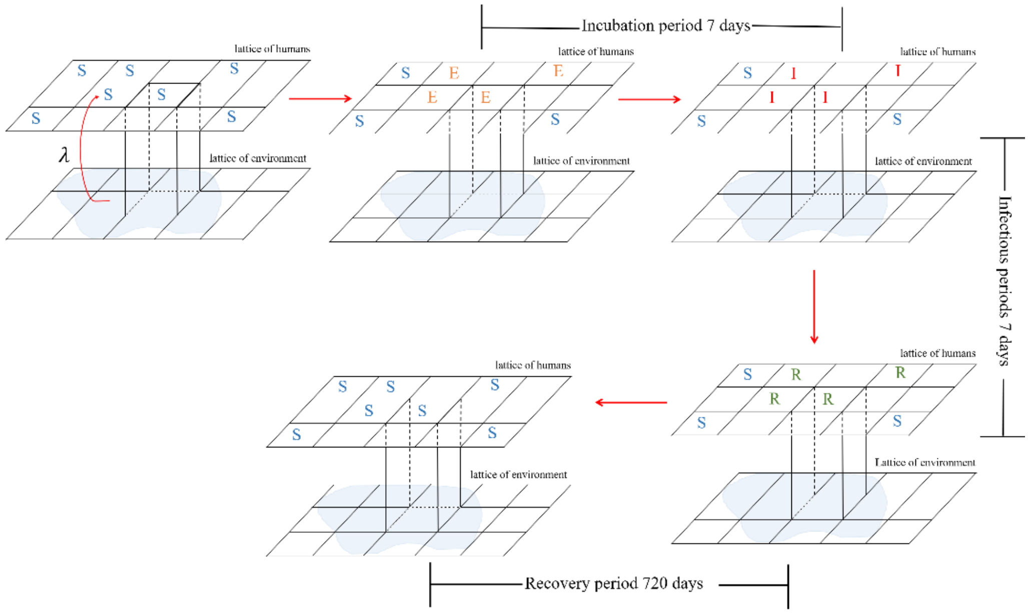

Figure 2. Schematic illustration of the transition state of the Stochastic Cellular Automata model.

Human mobility is considered primarily of large distance interaction diseases. Humans can move into infectious areas with the length distribution to the workplaces or other buildings leading to a high chance to be infected individuals. In each day, we randomly choose a human population leaves from its residence with probability ρ_{mob}. The selected human could move within the exponential step length distribution $P(r) = (r + \Delta r_0)^{-\beta} exp(-r/\kappa)$ with exponent β=1.75, Δr_0=1.5 km and cutoff values κ=80 km [38].

Due to the infected human presents the symptoms, we assumed that infected immobile. We confined that only S, E and R population can move to another site. People can move within the step length, which is determined by a random number following distribution with the maximum length of $M/2$. The angle is randomly chosen from a uniform distribution $[0, 2\pi]$. The parameters for the human population and mobility are shown in Table 2.

After human movement, if the position of the susceptible individual matches with the contaminated environment cell, the susceptible individual will gets infect with transmission rate (λ) to be exposed state. An exposed individual becomes an infected individual after a latent period of fixed length τ_E. An infected individual will infect for τ_I period then become a recovered state. This recovered individual will become an again susceptible period of fixed length τ_R.

To study the impact of MNDWI and rainfall, the transmission rate depends on the MNDWI ($W(t)$) and the rainfall index ($R(t)$) as in equation (3-4) compared to null hypothesis as a sinusoidal function (equation (2)). The transmission rate (λ) is assumed as a linear proportional of environmental variables to test different hypotheses given by:

$$\lambda_1(t) = n_0 + n_1(1 + \sin(2\pi t/365) - \tau) \quad (2)$$

$$\lambda_2(t) = n_0 + n_1(W(t) - \tau) \quad (3)$$

$$\lambda_3(t) = n_0 + n_1(R(t) - \tau) \quad (4)$$

where n_0 and n_1 are constant values. The reported data during 2014 and 2018 is used to fit with the simulation results. The parameters n_0 and n_1 were chosen, where the Mean Square Error (MSE) is minimized.

Table 2. Parameters for human and environmental lattices.

Description	Symbol	Values
Human population size	N_H	350,000
Daily rate of human mobility	ρ_{mob}	0.5 [39]
Water area density in environmental lattice	ρ_E	0.6
Incubation period for human	τ_E	7 days [40]
Duration of infection for human	τ_I	7 days [40]
Duration of loss immunity for human	τ_R	720 days (estimated)

5. Results

5.1 Results of statistical model

A total of 3,571 urine samples of cattle and buffalo were tested by the LAMP technique. 311 samples were positive. The overall uroprevalence over 107 districts is presented in figure 3. Positive samples were recorded in 51 districts (47.66% of districts). From the temporal aspect, higher prevalence was observed in May, which is the beginning of the rainy season in the central and northern part of Thailand [41].

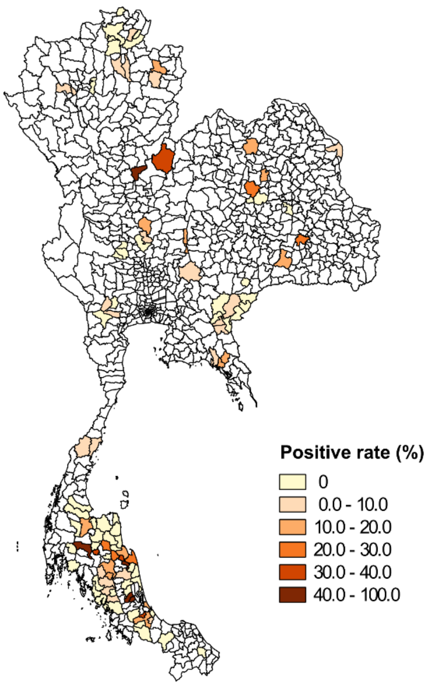

Figure 3. Map of the positive rate of leptospirosis in cattle and buffalo in 107 districts of Thailand. Urine samples were tested by LAMP. The non-sampled districts are presented in white.

The results of the univariate linear regressions show that the percentage of flooded area and the percentage of flooded area with a 1 month lag were found to be significant (Table 3). The risk of livestock infection was higher if the percentage of flood area was higher.

Table 3. Summary results of the univariable linear regression model (with binomial function and random effect).

Variable	Odd Ratio	95% Confidence Interval	p-value
Amount of rainfall at sampling day	0.9378	0.6588 - 1.2861	0.707
Cumulative of rainfall for 30 days	1.1205	0.8121 - 1.5020	0.466
Percentage of flood area	1.7129	1.1383 - 2.5942	0.009**
Percentage of flood area at 1 month lag	1.4770	1.0034 - 2.1994	0.047*
Average elevation	1.0118	0.6645 - 1.5262	0.966
Human population density	1.3258	0.9134 - 1.9130	0.133
livestock population density	0.6022	0.3082 - 1.1141	0.113

*p<0.05, **p<0.01

Three explanatory variables were kept in the final model based on the stepwise backward approach: the percentage of flooded area, human and livestock population densities (Table 4). This final model was applied to predict the risk of *Leptospira* presence at the district level, it showed high performance with an AUC of 0.8861 (figure 4). The percentage of flooded area was the only variable significantly associated with the prevalence of leptospirosis in cattle and buffalo in the GLMM (p = 0.023, Table 4). The cvAUC had a mean of 0.6427 (sd = 0.0827). The distribution of the 1,000 estimations of the cvAUC is shown in figure 5.

Table 4. Results of the best generalized linear mixed model as selected by a stepwise backward approach with the AIC.

Variable	Odd Ratio	95% Confidence Interval	p-value
Intercept	0.0309	0.0183 - 0.0473	<2e-16***
Percentage of flood area	1.5794	1.0611 - 2.3629	0.023*
Human population density	1.3495	0.9511 - 1.9016	0.084
Livestock population density	0.5989	0.3079 - 1.0957	0.105

*p<0.05, ***p<0.001

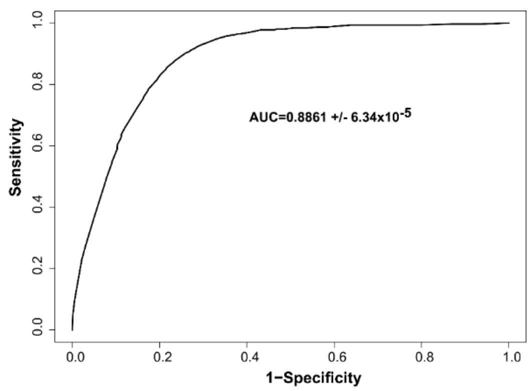

Figure 4. ROC curve of the best generalized linear mixed model.

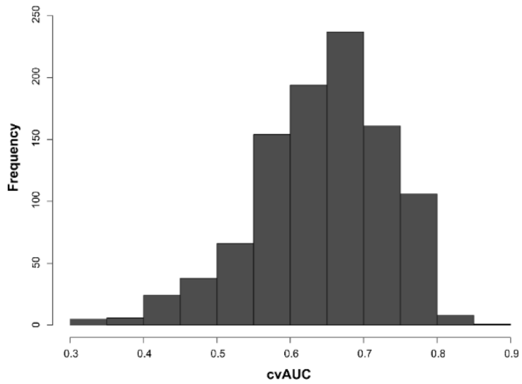

Figure 5. The cross-validated AUC distribution.

Maps of leptospirosis infection risk were produced from the final model in the middle of January, May, and September in 2012, which corresponds to the period when most data was collected (figure 6). As expected from the results of the model, the areas of increased leptospirosis risk vary seasonally (figure 6) and are found in the regions with a high percentage of area flooded. The districts with a high leptospirosis infection risk in mid-January were mostly located in the southern part of Thailand, especially in the south-east coastal regions, i.e. during the high rainfall period in this area [41]. In mid-May, high leptospirosis infection risk mostly occurs in northern and northeastern parts, which correspond to the beginning of the rainy season in this part of Thailand. In mid-September, high leptospirosis infection risk areas occurred in all parts except for the southern part, and was particularly high in the central part. In this analysis, the final model was also used to predict the leptospirosis infection risk in 2016. The leptospirosis infection risk districts were also mostly found in regions with a high percentage of flooded area.

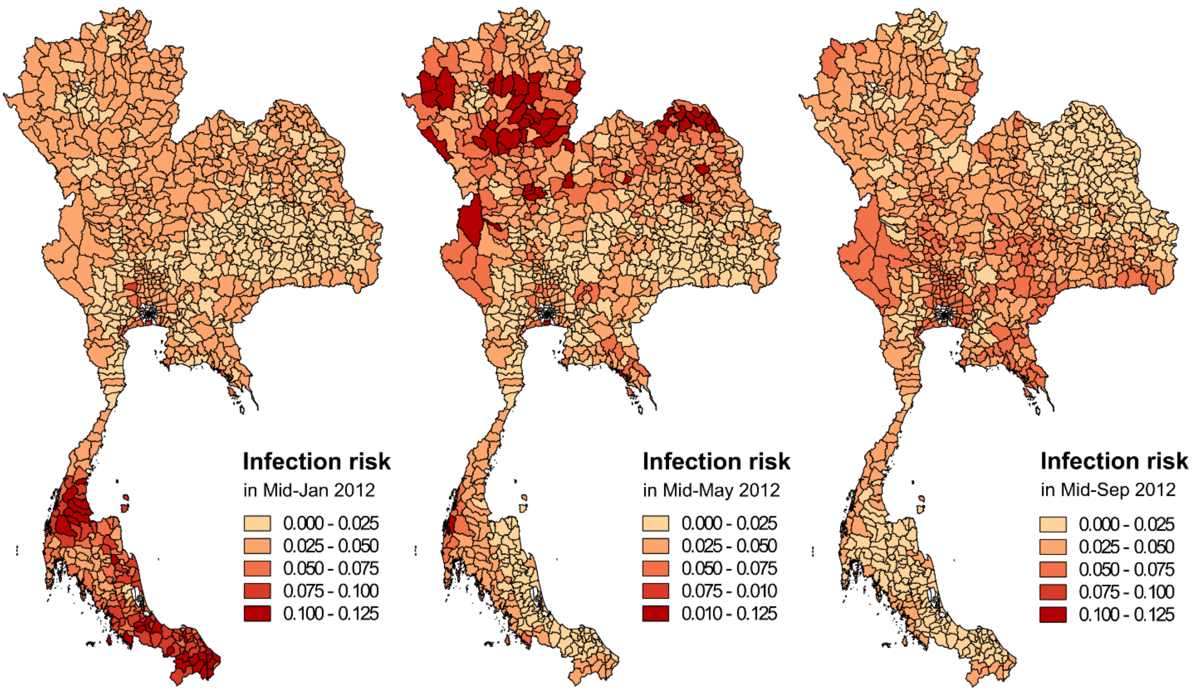

Figure 6. Map of the prediction of leptospirosis infection risk using the final multivariate linear regression model in three different periods of 2012. A leptospirosis infection risk of 0.1 indicates that approximately 1/10 livestock are expected to be positive by LAMP for leptospirosis infection. The non-predicted districts are presented in white.

5.2 Results of mathematical model

Based on the annual reports of leptospirosis cases in Thailand from 2010 to 2016, it appears that the disease continues to spread throughout the country (figure 7(A)). The highest number of annual cases was observed mostly in the northeastern region, which also had the highest number of cumulative cases (figure 7 (B)). In this work, we considered two provinces, namely, Si Sa Ket (highest number of cumulative cases) and Surin (second highest number of cumulative cases) for testing the models. The time series of reported biweekly cases were plotted with the percentage of flooding, the amount of rainfall, and temperature (figure 8). We found that the time series of biweekly reported cases in the two provinces showed a similar trend. The percentage of flooding and the amount of rainfall were found to increase around the same time of year when the number of reported cases increased. However, the temperature was negatively correlated with incident cases.

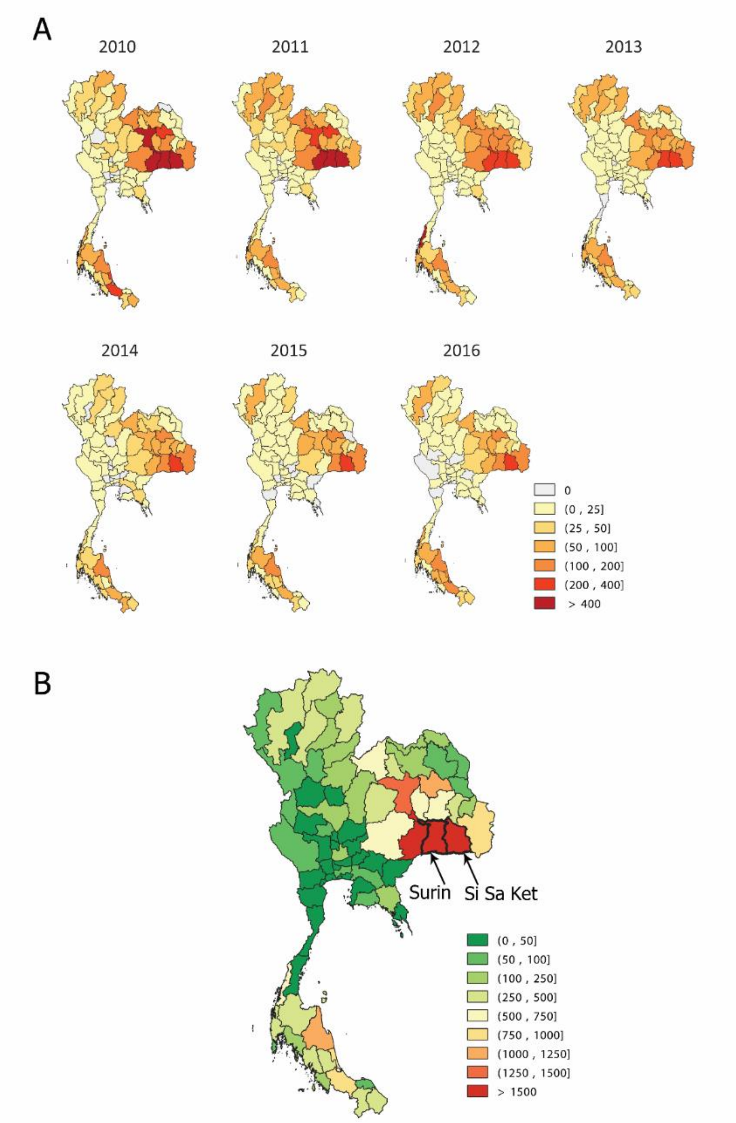

Figure 7. The map of reported cases in Thailand. The annual reported cases during 2010-2016 (A). The total reported cases during 2010-2016 (B).

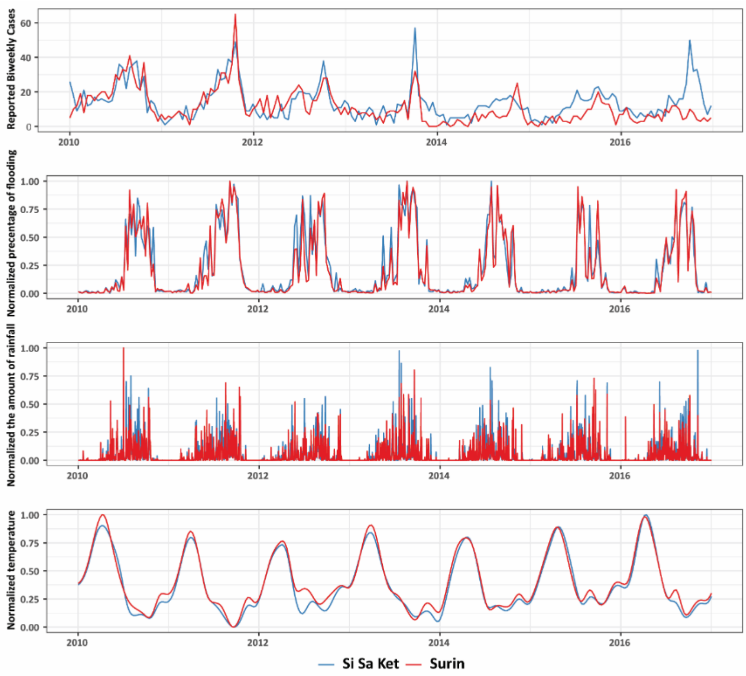

Figure 8. Data collection for 2 provinces.

Using the model described in the methods section, we fit eleven models (our ten models plus the null model) to the reported cases from 2010 to 2015 with time lags between 0-8 weeks for each province (figure 9). In general, we found that model 1 (M1) improved the fit, which indicated that making the transmission rate a linear function with environmental variables has an important impact on the infection dynamics in humans. Comparing the models incorporating flooding or rainfall factors (M1-F and M1-R), we found the model including the flooding factor fit better. The models that also included a temperature effect showed better performance. Overall, the model with the transmission rate dependent on flooding and temperature (M1-FT) had the lowest negative log-likelihood. Thus, we selected the M1-FT as the best-fit model for further analysis.

The M1-FT fitting and the stochastic simulation results, using the parameters shown in Table 5, are shown in figure 10. The stochastic output captures well the reported data. These results provide a reasonable fit with the predicted cases for 2016. Our model can provide more understanding on the transmission dynamics in contaminated environments.

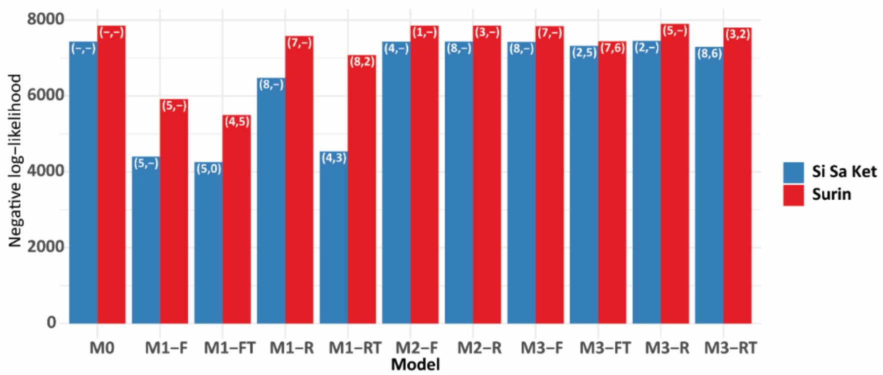

Figure 9. Bar chart of negative log-likelihood values for the ten models compared to a null model (M0) for the two provinces. The parentheses of each bar shows the time lag in week of flooding (rainfall) and temperature (t_1, t_2).

Table 5. A summary of the parameter estimates for the 2010-2015 leptospirosis epidemic in three provinces of the M1-FT model.

Symbol	Si Sa Ket	Surin
$\log(\beta_{ha})$	-5.833	-6.000
$\log(\beta_{aa})$	-2.518	-6.000
$\log(h_1)$	0.876	0.692
$\log(h_2)$	0.355	0.418
$\log(h_3)$	-0.467*	-0.228
$\log(a_1)$	-1.267	-6.000
$\log(a_2)$	-0.136	-1.510
$\log(a_3)$	-0.959*	-0.507*
$\log(\omega)$	-0.497	-6.000
$\log(m)$	0.538	0.586

*Negative number are provided on a normal scale

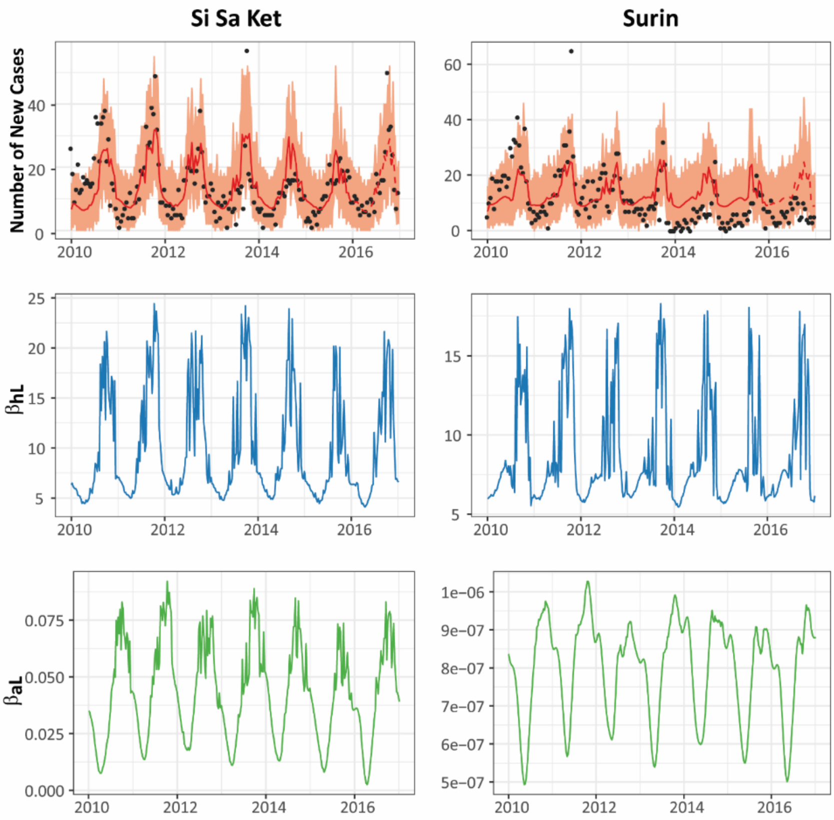

Figure 10. The fitted results of the M1-FT model (red line) compared to the reported cases of leptospirosis (black dot). The orange shaded area displays 1,000 curves of the stochastic simulations. The red dashed line represents the predicted cases for 2016. The time-dependent transmission rate from the contaminated environment to susceptible human and susceptible livestock (β_{hL} and β_{aL}) correspond to values in Table 5 are shown in the blue and green lines, respectively.

The transmission rate from the contaminated environment to humans and livestock is plotted versus time according to the flooding and temperature factors (figure 10). The average transmission rate from the contaminated environment to humans (β_{hL}) over time is 9.886 and 8.737 for Si Sa Ket and Surin. This corresponds to a decline in the total number of reported cases during the dry season. The transmission rate from the contaminated environment to livestock (β_{aL}) also varied with time. It was higher in Si Sa Ket and lower in Surin. However, the β_{hL} was always the highest transmission rate. This result indicated that the main reason for human infection is due to the transmission of leptospires from the contaminated environment, rather than from contact with infected animals. Comparing the coefficients of β_{hL}, the flooding indicator had the most impact on transmission, which indicates a high amount of flooded area leads to higher cases.

The fitting results indicate that our model is capable to reproduce the incidences of the leptospirosis epidemic, using the seasonal changes of the amount of flooded area as an indicator of increased infection rates. The number of new infection cases can be predicted during winter, depending on the parameters calculated in the given areas.

In this work, we estimated the time-dependent reproduction number (R_{td}) for two provinces with the 95% confidence interval using the simulation results as shown in figure 11. We found the R_{td} oscillated around 1.0 which suggests it is an endemic disease, as expected for leptospirosis in Thailand. The mean (sd) of R_{td} is estimated at 1.020 (0.198) and 1.011 (0.158) for Si Sa Ket and Surin. A similar pattern of R_{td} was observed for both provinces in the same region in the simulated cases. Note that this estimation was based on the observed human cases. Normally, leptospirosis has a basic reproduction number close to zero due to its minimal transmissibility among human population. However, this estimation could provide a better picture of how leptospirosis transmits from animal sources and contaminated environments to humans.

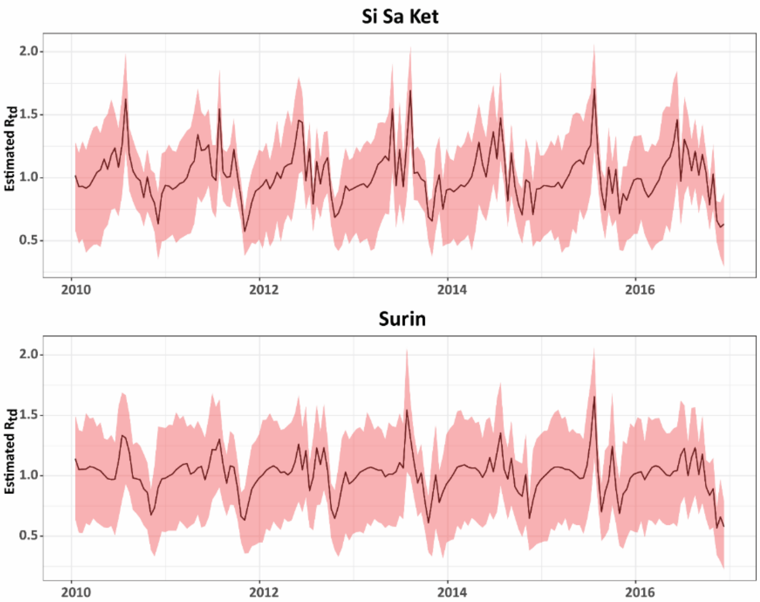

Figure 11. The estimated R_{td} for the two provinces plotted with the 95% confidence interval.

As no vaccine or specific medicines are available for leptospirosis, the most important strategy to control the disease is to decrease the transmission rate. Figure 12 shows the PRCC values with 95% CI, obtained for the ten parameters in Table S1. Absolute PRCC values greater than 0.3 are considered important parameters. We found that the parameters of β_{hL} (h_1, h_2 and h_3) were the most important on the total number of cases for all provinces. Our results also suggest how decreasing the transmission rate of leptospirosis from the contaminated environment to human can affect the leptospirosis dynamics to reduce the number of human cases. Figure 13 shows how the number of human cases can be reduced as the transmission rate of β_{hL} is reduced. A 90% reduction ($0.9\beta_{hL}$) could reduce the total number of human cases by about 90%. Considering the overall results, this study suggests that we should avoid contacting contaminated environments during flooding.

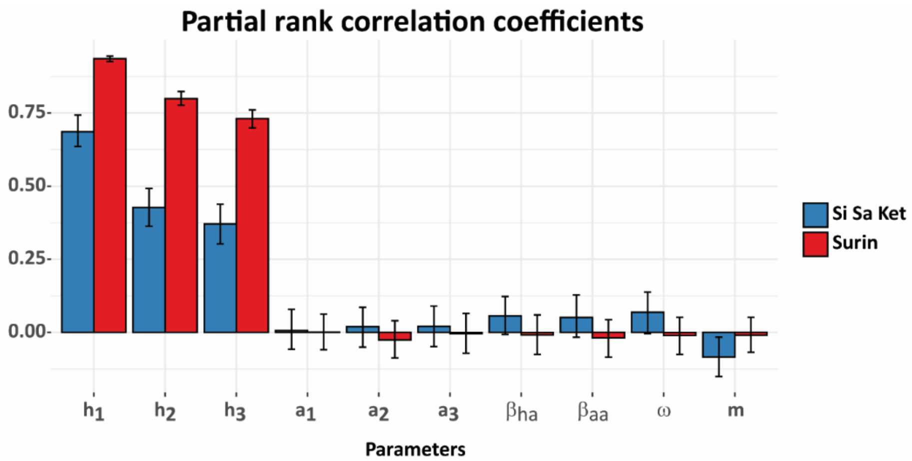

Figure 12. Partial rank correlation coefficients of the ten parameters and the total number of cases, plotted with an error bar showing the 95 % confidence interval. The h_i and a_i are constant values to calculate the transmission rates β_{hL} and β_{aL}, respectively.

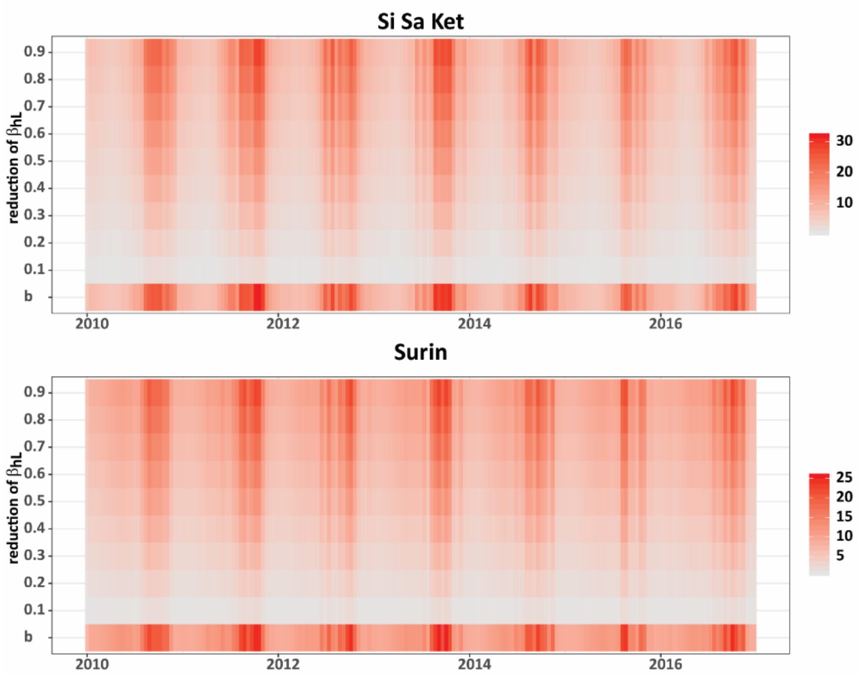

Figure 13. The number of human cases as the transmission rate from the contaminated environment to human (β_{hL}) of M1-FT is varied between $0.1\beta_{hL}$ to $0.9\beta_{hL}$, where b is the baseline.

5.3 Results of Stochastic Cellular Automata model

In this part, we aimed to use the lattice-based model of leptospirosis for human infection via environment using seasonal fluctuation in Si Sa Ket. We developed the Stochastic Cellular Automata model consist of human and environmental lattice. Figure 14 showed the relation between reported cases of leptospirosis, normalized MNDWI, normalized rainfall index, and sinusoidal function. The number of reported cases all year round showed a seasonality pattern, which have high cases occurred during August and October correspond to the rainy season. We found the peak of reported cases correspond to the peak of MNDWI, rainfall index and sinusoidal curve with some time lag.

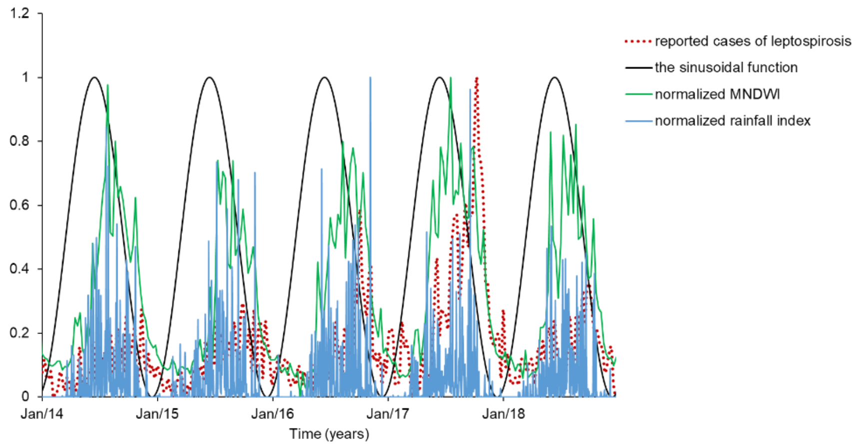

Figure 14. The relation between reported cases of leptospirosis, the sinusoidal function, normalized MNDWI and normalized rainfall index for 2014-2018.

We varied time lag of the sinusoidal function, found that time lag of 4 weeks consistent with reports cases. We compared the real data and simulation results using mean square error (MSE), which found the minimized of MSE equal to 64.30 (figure 15). However, this function captured the reported cases only for the small value. The simulation result of the transmission rate depends on rainfall index with the associations observed at time lag of 2 weeks, which correspond to previous study [42]. The peak of leptospirosis cases corresponds with the peak of simulation results in almost every year. However, it could not describe the data on 2017 due to the other factor such as monsoon and heavy rainfall [43]. In fitting process, our results suggested that using rainfall index fit better than a sinusoidal function, which found MSE equal to 47.35. For the transmission rate varied with MNDWI, we found the best fit of 1 week time lag with MSE equal to 36.75. The plot of figure 15 clearly showed that the MNDWI fit with the reported better than rainfall index and sinusoidal function. This finding indicated that the MNDWI contributed to the transmission dynamics of leptospirosis. Although, the sinusoidal function has been commonly used to represent seasonality in epidemic models [44].

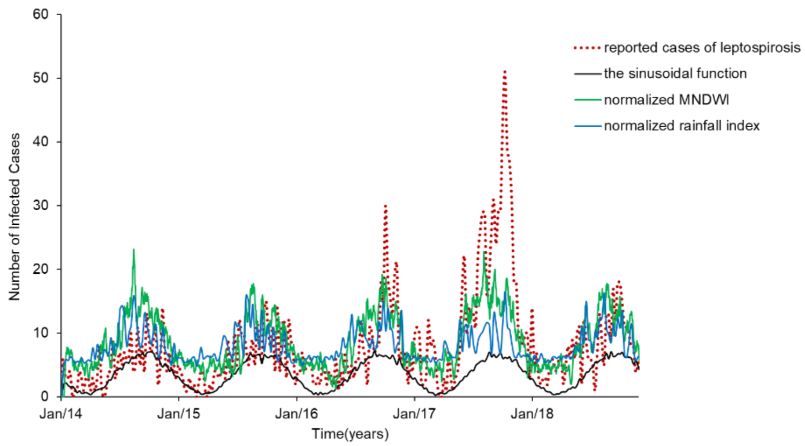

Figure 15. The reported cases of leptospirosis and the simulation result prediction of the transmission depend on the sinusoidal function with $n_0 = 3.47 \times 10^{-7}$ and $n_1 = 2.09 \times 10^{-6}$, the MNDWI with $n_0 = 2 \times 10^{-6}$ and $n_1 = 1 \times 10^{-6}$, and the rainfall index with $n_0 = 4.01 \times 10^{-6}$ and $n_1 = 3.21 \times 10^{-5}$.

In various types of epidemic models, it has been the central issue of how the final epidemic size is determined by the individual system parameters or the composite of them [45]. In this study, we defined the final epidemic size as the fraction of recovered at steady state. To investigate the transmission rate contributes to the final epidemic size in our model, we set the transmission rate be a constant value ($\lambda = n_0$). The critical transmission rate is showed in figure 16, suggests that phase transition from endemic phase to epidemic state.

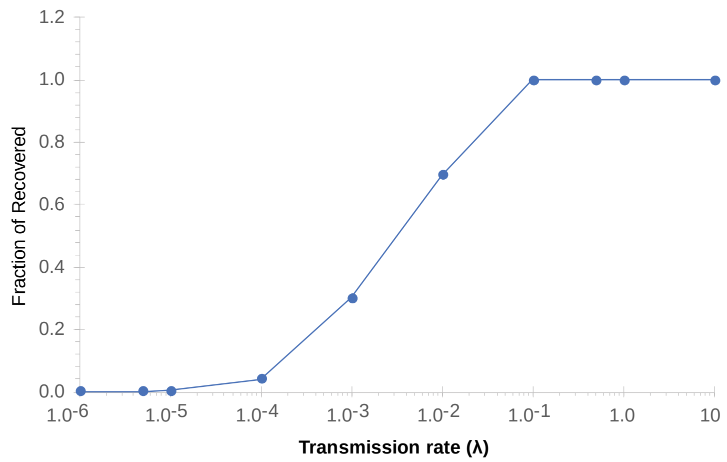

Figure 16. The final epidemic size as predicted by the SEIR model is shown with respect to the transmission rate.

6. Conclusion and Discussion

Using statistical model, our results show a significant association between the percentage of flood area and leptospirosis infection in cattle and buffalo at the district level. The flooding area was evaluated using a remote sensing indicator [8, 9]. This finding suggests that exposure to flooding increases the risk of leptospirosis infection for cattle and buffalo. Most of the samples used in this study were collected in rural areas. In these areas, the soil may become contaminated with leptospires because of the presence of infected animals. When flooding or heavy rainfall occurs, the water picks up contaminated soil and animal excreta from the soil. This results in the spread of leptospirosis through contaminated water [46, 47]. Flooding could possibly be the principal reason for leptospirosis epidemics above other factors [48]. This is consistent with other studies showing that local flooding can play an important role in leptospirosis transmission [9, 48, 49]. Therefore, flood control could be an option to reduce the risk of leptospirosis infection in animals, which can be a major reservoir for human infection [1, 50].

Furthermore, the results of the univariate linear regressions show that the flooding factor is the only significant factor and is a better indicator than the amount of rainfall and the accumulation of rainfall. It may be because rainfall does not directly influence leptospirosis transmission while flooding facilitating it. Rainfall has previously been associated with leptospirosis but often with a time lag of 1-3 months [28, 29] which is likely the lag between rainfall and flooding. A remotely sensed flooding indicator is likely to be a more accurate predictor of the risk of leptospirosis infection than using rainfall.

The predicted risk maps of leptospirosis infection were created based on the final model for 3 periods in 2012. In each part of Thailand, higher infection risk was observed during the first floods after a dry period in that part of the country. This influence of the first flood of the year has been suggested in other studies [9]. It could be responsible for the rapid dissemination of leptospires concentrated in small areas during the dry season. High prevalence in livestock is not predicted in the same period for the whole Thailand. Three main periods of risk can be identified and associated with three different parts of Thailand (i.e., Northern, Central and Southern parts) and are related with the periods of flooding. The difference in these flooding periods is mainly due to two factors: a) the difference of rainfall seasonality between southern Thailand and the rest of the country, and b) the delay between rainfall and flooding between the central part and the northeastern part of the country. The central part of the country is downstream of the most important rivers in Thailand, and major flooding occurs later than in the rest of the country, in September to November, with an increased intensity. This explains why high risk occurs for most districts in this period, which also corresponds to its high population [37].

With the backward step approach, the final model includes human and livestock population densities. However, the model results show that those variables are not significant. Furthermore, these variables should be interpreted very cautiously because several confounding factors could be involved. Thus, they were kept because they improved the final model (based on the decrease of the AIC), but they should not be over-interpreted.

Our study was based on a cross-sectional survey [1], which was limited as there may be procedural concerns. It does not provide data for all districts in the country and for all seasons in each district. A longitudinal survey is strongly suggested in further studies, with repeated sampling in a larger number of districts in the whole country. It would provide better data to understand the seasonality of leptospirosis infection and could provide a more accurate disease transmission model. The samples in each district were mostly collected only once. However, the samples were distributed over every part of Thailand for all seasons. Furthermore, the model had a relatively good performance (AUC =0.8861) but a lower and quite variable cross-validated AUC (mean cvAUC = 0.6427, sd= 0.0827, Figure 3). This difference between AUC and cvAUC, and the variability of the cvAUC may be explained by the relatively small size of our dataset at the district level leading to a small validation dataset (71 districts for the training dataset and only 36 for the validation dataset). Furthermore, given this size limit, some validation datasets may include a different proportion of southern districts than their matching training datasets. The difference of flooding patterns between southern Thailand and the rest of the country may then further explain the lower cvAUC. Training the model on a larger dataset and having an independent large dataset to validate it would help build a more robust model.

Using mathematical models, that include environmental data are presented and used to describe the transmission of leptospirosis in two provinces in the northeastern region of Thailand. This work presents the first attempt to incorporate environmental data into the mathematical models of leptospirosis transmission. The annual change of the environmental data can describe the seasonal epidemic with higher prevalence during the rainy season for the northeastern region, than a model not incorporating any environmental data.

Our finding suggests that transmission from a contaminated environment, as opposed direct contact with an infected animal, is the best model. This study is novel by finding that the amount of flooded area in a region, which obtained from a remotely sensed data, is the most important factor for leptospirosis transmission to humans. This implies that including a leptospires compartment, which refers to the number of pathogenic bacteria in the contaminated environment, reasonable describes the infection of humans during an endemic.

Previous studies have pointed out that leptospires survive and persist in the environment, both water and soil, for several weeks [51]. Environmental survival of pathogens can be an important parameter in epidemiology. During heavy rain with increased flooded areas, leptospires in the environment have more chances to enter the human body via cut skin. Working or living in flooded areas has been identified as a significant factor for increasing the contraction of leptospirosis [52]. Analysing our model, after fitting to human data from 2010-2015, the amount of flooded area was shown to be more important to improve the model as compared to the rainfall. Our results are consistent with a previous study that observed animals in Thailand from 2011–2013 [53]. This indicates that flooding is a factor that influences the epidemiology of leptospirosis in both humans and animals. Flooding was also observed to be an important risk factor in other countries such as Argentina [54], Brazil [55] and Malaysia [56]. In our study, including the effect of temperature in the model improved the transmission model a modest amount. The temperature may affect leptospire virulence [25], and the transmission rate. The temperature effect observed in our study is in line with previous studies [57-59].

In this study, the time-dependent reproductive number was estimated for leptospirosis in humans. Normally, the basic reproductive number (R_0) cannot be estimated in humans due to minimal transmission between humans. However, in our case, we focused on how the transmission occurred in humans in term of R_{td}. Our model's estimation highlights that leptospirosis occurs mainly during mid-year for provinces in northeastern region.

From the PRCC analysis of our model, the transmission rate of leptospires to humans is most effected by the total number of cases. A disease control method, according to the PRCC results, suggest avoiding flooded areas, to reduce the transmission rate during an outbreak [60]. And protective equipment, such as wearing boots or gloves, is recommended when in contact with flooded areas.

Using spatial model as SCA model, our results confirmed that the MNDWI is the best factor to explain the transmission dynamics between human and environment. The epidemic of leptospirosis are known to be a seasonal pattern. Rainfall is an important risk factor for leptospirosis outbreaks and strongly associated with the tropical settings [20, 61, 62]. The heavy rainfall washes superficial soils, bringing pathogenic leptospires in freshwater bodies, where humans will be exposed. Massive leptospirosis outbreaks usually emerge following waterlogging. After heavy rainfall, this pathogen can survive for days to months in a contaminated environment [63].

In conclusion, our findings could identify flooding as a major driver of the risk of leptospirosis infection in cattle and buffalo. The leptospirosis transmission model predicts the significant environment factor associated with leptospirosis transmission is flooding as well as SCA model. Public awareness about the risk of leptospirosis during flooding should be raised in order for people to take prevention measures when possible. The risk maps could also help to develop effective intervention strategies and optimize the allocation of public health resources, veterinary care and control measures. High level of livestock infection could increase the risk to human health due to contact with infected animals or contact via to contaminated environment by the urine of infected animals [23, 64]. Livestock may then play an important role as a potential indicator of high risk areas for leptospirosis in humans. A reduction in contact with a contaminated environment can help to improve disease control. This work can be applied to other leptospirosis epidemic areas where flooding data is provided. Further studies should be carried out to access the role of livestock and other relevant data on the transmission of leptospires. Climate change or extreme weather events can also be modelled to predict the severity of future leptospirosis outbreaks [65]. Based on our results, public health policy maker may guide the people who work close to, or in contaminated environments to avoid potential sources of leptospirosis, or by protecting themselves by wearing boots to reduce the leptospirosis outbreak.

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7. Appendix

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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

A remotely sensed flooding indicator associated with cattle and buffalo leptospirosis cases in Thailand 2011–2013

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Abstract

Background: Leptospirosis is an important zoonotic disease worldwide, caused by spirochetes bacteria of the genus *Leptospira*. In Thailand, cattle and buffalo used in agriculture are in close contact with human beings. During flooding, bacteria can quickly spread throughout an environment, increasing the risk of leptospirosis infection. The aim of this study was to investigate the association of several environmental factors with cattle and buffalo leptospirosis cases in Thailand, with a focus on flooding.

Method: A total of 3571 urine samples were collected from cattle and buffalo in 107 districts by field veterinarians from January 2011 to February 2013. All samples were examined for the presence of leptospirosis infection by loop-mediated isothermal amplification (LAMP). Environmental data, including rainfall, percentage of flooded area (estimated by remote sensing), average elevation, and human and livestock population density were used to build a generalized linear mixed model.

Results: A total of 311 out of 3571 (8.43%) urine samples tested positive by the LAMP technique. Positive samples were recorded in 51 out of 107 districts (47.66%). Results showed a significant association between the percentage of the area flooded at district level and leptospirosis infection in cattle and buffalo ($p = 0.023$). Using this data, a map with a predicted risk of leptospirosis can be developed to help forecast leptospirosis cases in the field.

Conclusions: Our model allows the identification of areas and periods when the risk of leptospirosis infection is higher in cattle and buffalo, mainly due to a seasonal flooding. The increased risk of leptospirosis infection can also be higher in humans too. These areas and periods should be targeted for leptospirosis surveillance and control in both humans and animals.

Keywords: Leptospirosis, Flooding, Buffalo, Cattle, Thailand, Satellite imagery

Background

Leptospirosis is an important worldwide zoonotic disease, caused by spirochetes bacteria of the genus *Leptospira* [1, 2]. This bacteria is classified into pathogenic and nonpathogenic species, with more than 250 pathogenic serovars [1–3]. The disease is particularly important in tropical and subtropical countries. Human and animal infections can occur through direct exposure to infected animals or to indirect exposure to the soil or water contaminated with urine from an infected animal through skin abrasions or mucous membranes [1, 2].

In livestock, it is considered one of the most important diseases, particularly in cattle due to reproductive failures (such as abortion, embryonic death, stillbirths and weak off-spring), decreased milk production and growth rates [1, 4–6]. This results in significant economic losses [7] given the importance of these animals in tropical countries. In Thailand, about 4.4 million beef cattle, 0.51 million dairy cattle, and 0.89 million buffaloes were raised by 770,000, 160,000 and 200,000 households in 2012, respectively [8]. In rural areas, cattle and buffalo live in close contact with agricultural workers, and can

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be a major source of leptospirosis in humans, as highlighted by the predominance of the same serovars in both livestock and humans [4, 9]. Furthermore, a relatively high prevalence of leptospirosis have been detected in the urine of cattle and buffalo in Thailand [10]. An important route of transmission of *Leptospira* from livestock to humans could then be through contaminated urine [1, 2]. And as a consequence, flooding may be an important factor facilitating the transmission of *Leptospira* from livestock to humans and other animals by facilitating the spread of bacteria in wet soils and surface water, where the bacteria can survive for several weeks or months [11].

In humans, the number of reported leptospirosis cases in Thailand is highest after the peak in the rainy season [12]. Higher numbers of leptospirosis cases have been reported following rain or flooding in tropical and subtropical areas (e.g., Laos [13], Guyana [14], and Sri Lanka [15]). In Thailand, most reported cases occurred in northern and northeastern regions, where the main occupation is rice farming. Agricultural workers are the most exposed to biological contaminates in the environment. A previous study in Thailand found that human leptospirosis infections were observed near rivers, and mostly in rice fields likely to have flooding [16]. Furthermore, heavy rain and flooding have been identified as environmental drivers of leptospirosis infections in animals [17]. In the same way, leptospirosis infection risk is associated with flooding in Laos, particularly for human beings who have behaviors and activities involving contact with floodwater [13]. Overall, flooding appears as an important driver of leptospirosis infection in both humans and animals. By taking into account the seasonal variations of flooding using remotely sensed indicators, it may help in anticipating the risk of leptospirosis infection and identify periods and areas for increased surveillance and prevention [18].

The main objective of this study was to investigate the association of several environmental factors (especially remotely sensed indicators of flooding) with cattle and buffalo leptospirosis cases in Thailand. A model of leptospirosis infection risk at the district level was produced, taking into account seasonal flooding.

Materials and methods

Epidemiological data

A total of 3571 urine samples derived from 488 buffalo and 3083 cattle, were collected from January 2011 to February 2013 under a cross-sectional program, which has been described in detail in a recent article [4]. The sampling process was prepared by the provincial Department of Livestock Development livestock officers in 107 districts from 28 provinces, and the samples were randomly selected from each region of Thailand [4]. The sample size was calculated using the multi-stage clustered sampling technique. Three provinces in each of the 9 livestock administrative regions were chosen to represent the area. Subsequently, districts within the provinces were sampled. The target sample size in each region was calculated with the method proposed by Yamane [19]. In this study, we combined 9 regions of Thailand into 4 parts with different climate and seasonal flooding patterns, i.e. the Northern part, subdivided into the Upper Northern and Lower Northern, Central part, which consists of Central, Western and Eastern sub-regions, Northeast part, which consist of Upper Northeastern and Lower Northeastern regions, and the South, which consist of Upper Southern and Lower Southern regions. In their study, the number of samples in each district was not controlled. Sampling was not systematically repeated in all districts, but data was collected during the whole year in the different districts. All urine samples were examined for the presence/absence of leptospiral infection by loop-mediated isothermal amplification (LAMP) method [4, 10]. This technique showed high sensitivity and specificity at 96.8 and 97.0%, respectively [10].

Environmental data

The environmental variables tested in our study include rainfall, flooded area, elevation, and human and livestock population densities. Flooding is an important driver of leptospirosis, but no data is readily available. The flooding variable was calculated based on the modified normalized difference water index (MNDWI). Other variables were collected from national or international databases. All variables were aggregated at the district level to match the spatial resolution of the epidemiological data.

The amount of rainfall was obtained from near Real-time TRMM (Tropical Rainfall Measuring Mission) multi-satellite precipitation analysis (TMPA-RT), which is produced at the National Aeronautics and Space Administration, Goddard Earth Sciences Data and Information Services Center (NASA GES DISC) [20]. The daily accumulated precipitation product is generated from the Near Real-Time Precipitation 3-hourly 1 day TMPA at a spatial resolution of 0.25 degree × 0.25 degree Version 7 (TRMM 3B42RT Daily) [21, 22]. In this study, given the homogeneity of rainfall at the district level, we only extracted the TRMM data at the centroid of each district.

To identify flooded areas, we used the data from the Moderate Resolution Imaging Spectroradiometer (MODIS) of the Terra satellite (Surface Reflectance 8-Day L3 Global 500 m SIN Grid V005 (MOD09A1)). In each image pixel, the data provides an estimation of the surface spectral reflectance measured at ground level in the absence of atmospheric scattering or absorption. The band 4 (green) and band 7 (infrared) were used to calculate the modified normalized difference water index (MNDWI) [18, 23], which allows an estimate of the water presence in each pixel. Within all districts, each pixel was classified as flooded if the MNDWI value was more than or equal to zero. This threshold of zero for MNDWI is in the range of optimal thresholds calibrated in previous studies [23–25]. Permanent water bodies such as rivers and lakes were masked out using QGIS version 2.8.3 [26]. Then, the number of flooded pixels were counted to calculate the percentage of flooded land in each district.

Elevation can be associated with slopes and increased movement of surface water [27], but slope data was not available at a national scale in Thailand. Elevation data was derived from the NASA Shuttle Radar Topographic Mission (SRTM) 90 m Digital Elevation Data, which provides elevation data for the entire world (http://srtm.csi.cgiar.org/index.asp). The average elevation at the district level was used in the model.

Human population data was obtained from the WorldPop database, which presents the number of people per hectare (http://www.worldpop.org.uk) (Additional file 2: Figure S5). Human population density was included in the model because it could be associated with different agricultural practices in areas with different levels of economic development. The animal population density of livestock species (buffalo, cattle, goat, pigs and sheep) were obtained from the Information and Communication Technology Center (ICT), Department of Livestock Development of Thailand at the district level (http://ict.dld.go.th) (Additional file 2: Figure S5). Goats, pigs and sheep were included because they may also contribute to the circulation of leptospirosis in cattle and buffaloes. Seroprevalences of other livestock were shown in Thailand from January to August 2001 in a previous study [28]. In this study, no urine samples were collected in urban districts because limited number of cattle and buffaloes are found in areas of high human population density. The districts with a human population density above 1400 people/km^2, which corresponds to the urban centers of the main cities of Thailand, and no livestock were not included in the risk mapping given the limited number of animals in urban centers.

Statistical analysis

To investigate the association between the risk factors listed in the previous paragraph (explanatory variables with a fixed effect) and leptospirosis infection (the response variable), we first study univariate linear regressions. Using a generalized linear mixed model (GLMM) with a logit link since the response variable had a binomial distribution. We used R software [29] with the package lme4 [30]. Since all individual urine samples were not independent because they were collected during common sampling occasions, we used the sampling occasion index as a random effect variable. Each sampling occasion was identified by a date, a year and a district geocode. The best multivariable model was selected using a stepwise backward approach based on the Akaike Information Criterion (AIC). The Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC) plot was used to estimate the model performance. We also used cross-validation to measure the performance of the best model. Data was randomly split into training (2/3 of data) and test (1/3 of data) sets. Training data is used to produce the prediction model, while the test data is used to test the model performance. Given the size of our dataset, we chose to keep 2/3 of the data in the training set to optimize model performance. We performed repeated cross-validations 1000 times to estimate the mean and standard deviation of the cross-validated AUC (cvAUC) of the best model.

The best model was used to predict leptospirosis infection risk in 2012 and 2016 for three periods (mid-January, mid-May and mid-September) which represents the middle of the dry season, the beginning of the rainy season and the end of the rainy season, respectively for central and northern Thailand.

Results

A total of 3571 urine samples of cattle and buffalo were tested by the LAMP technique. 311 samples were positive. The overall uroprevalence over 107 districts is presented in Fig. 1. Positive samples were recorded in 51 districts (47.66% of districts). From the temporal aspect, higher prevalence was observed in May (Fig. 2), which is the beginning of the rainy season in the central and northern part of Thailand [31].

The results of the univariate linear regressions show that the percentage of flooded area and the percentage of flooded area with a 1 month lag were found to be significant (Additional file 1:Table S1). The risk of livestock infection was higher if the percentage of flood area was higher.

Three explanatory variables were kept in the final model based on the stepwise backward approach: the percentage of flooded area, human and livestock population densities (Table 1). This final model was applied to predict the risk of *Leptospira* presence at the district level, it showed high performance with an AUC of 0.8861 (Fig. 3). The percentage of flooded area was the only variable significantly associated with the prevalence of leptospirosis in cattle and buffalo in the GLMM ($p = 0.023$, Table 1). The cvAUC had a mean of 0.6427 (sd = 0.0827). The distribution of the 1000 estimations of the cvAUC is shown in Fig. 4.

Maps of leptospirosis infection risk were produced from the final model in the middle of January, May, and

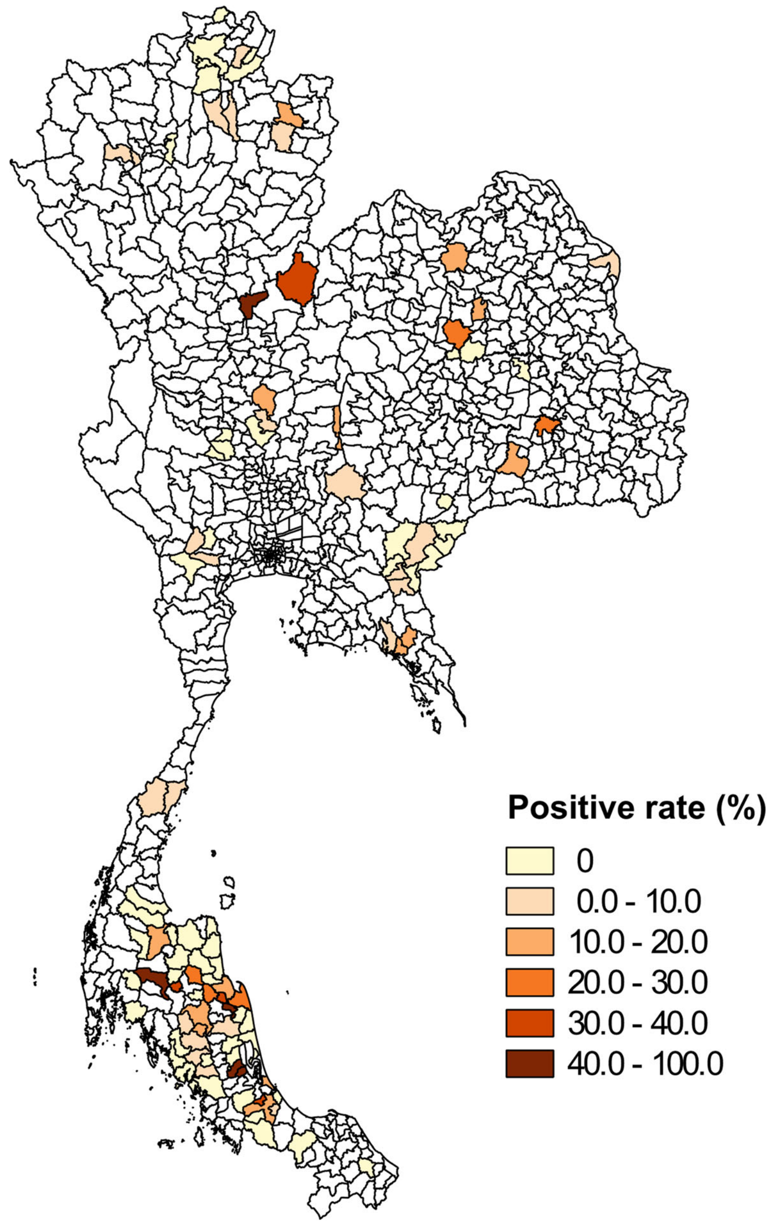

Fig. 1 Map of the positive rate of leptospirosis in cattle and buffalo in 107 districts of Thailand. Urine samples were tested by LAMP. The non-sampled districts are presented in white

September in 2012, which corresponds to the period when most data were collected (Fig. 5). As expected from the results of the model, the areas of increased leptospirosis risk vary seasonally (Fig. 5) and are found in the regions with a high percentage of area flooded (Additional file 2: Figure S1). The districts with a high leptospirosis infection risk in mid-January were mostly located in the southern part of Thailand, especially in the south-east coastal regions, i.e. during the high rainfall period in this area (Additional file 2: Figure S2) [31]. In mid-May, high leptospirosis infection risk mostly occurs in northern and north-eastern parts, which correspond to the beginning of the rainy season in this part of Thailand. In mid-September, high leptospirosis infection risk areas occurred in all parts except for the southern part, and was particularly high in the central part. In this analysis, the final model was also used to predict the leptospirosis infection risk in 2016 (Additional file 2: Figure S3). The leptospirosis infection risk districts were also mostly found in regions with a high percentage of flooded area (Additional file 2: Figure S4).

Discussion

This study investigates the relation between cattle and buffalo leptospirosis infections and flooding based on

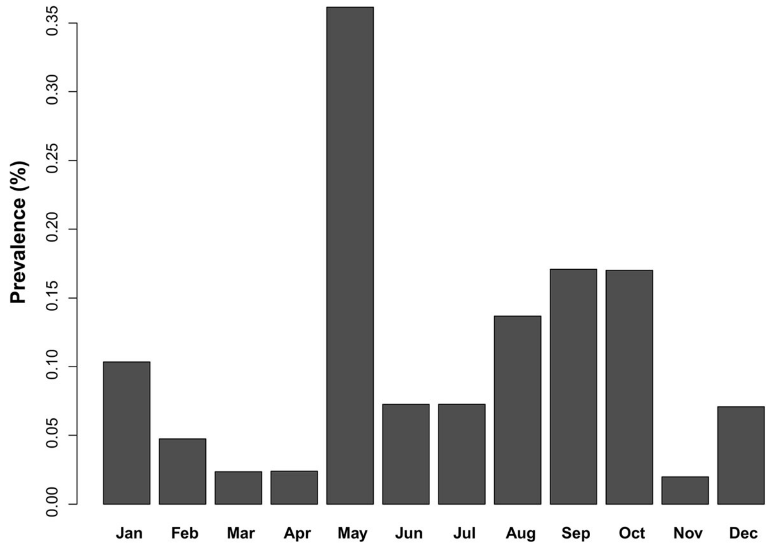

Fig. 2 The leptospirosis prevalence observed per month in both cattle and buffalo for 2011–2013

cross-sectional surveillance during 2011–2013 in Thailand. This analysis provides, to our knowledge, the first predictive risk mapping for cattle and buffalo leptospirosis in Thailand. The temporal and spatial variations of leptospirosis infection in Thailand appears to be associated with flooding.

Results of the GLMM show a significant association between the percentage of flood area and leptospirosis infection in cattle and buffalo at the district level. The flooding area was evaluated using a remote sensing indicator [18, 23]. This finding suggests that exposure to flooding increases the risk of leptospirosis infection for cattle and buffalo. Most of the samples used in this study were collected in rural areas. In these areas, the soil may become contaminated with leptospires because of the presence of infected animals. When flooding or heavy rainfall occurs, the water picks up contaminated soil and animal excreta from the soil. This results in the spread of leptospirosis through contaminated water [32, 33]. Flooding could possibly be the principal reason for leptospirosis epidemics above other factors [34]. This is consistent with other studies showing that local flooding can play an important role in leptospirosis transmission [17, 18, 34]. Therefore, flood control could be an option to reduce the risk of leptospirosis infection in animals, which can be a major reservoir for human infection [4, 9].

Furthermore, the results of the univariate linear regressions show that the flooding factor is the only significant factor and is a better indicator than the amount of rainfall and the accumulation of rainfall. It may be because rainfall does not directly influence leptospirosis transmission while flooding facilitating it. Rainfall has previously been associated with leptospirosis but often with a time lag of 1–3 months [35, 36] which is likely the lag between rainfall and flooding. A remotely sensed flooding indicator is likely to be a more accurate predictor of the risk of leptospirosis infection than using rainfall.

The predicted risk maps of leptospirosis infection were created based on the final model for 3 periods in 2012. In each part of Thailand, higher infection risk was observed during the first floods after a dry period in that part of the country. This influence of the first flood of the year has been suggested in other studies [18]. It could be responsible for the rapid dissemination of leptospires concentrated in small areas during the dry season. High prevalence in livestock is not predicted in the same period for the whole Thailand. Three main periods

Table 1 Results of the best generalized linear mixed model as selected by a stepwise backward approach with the AIC

Variable	Odd Ratio	95% Confidence Interval	*p*-value
Intercept	0.0309	0.0183–0.0473	<2e-16***
Percentage of flood area	1.5794	1.0611–2.3629	0.023*
Human population density	1.3495	0.9511–1.9016	0.084
Livestock population density	0.5989	0.3079–1.0957	0.105

*$p < 0.05$, ***$p < 0.001$

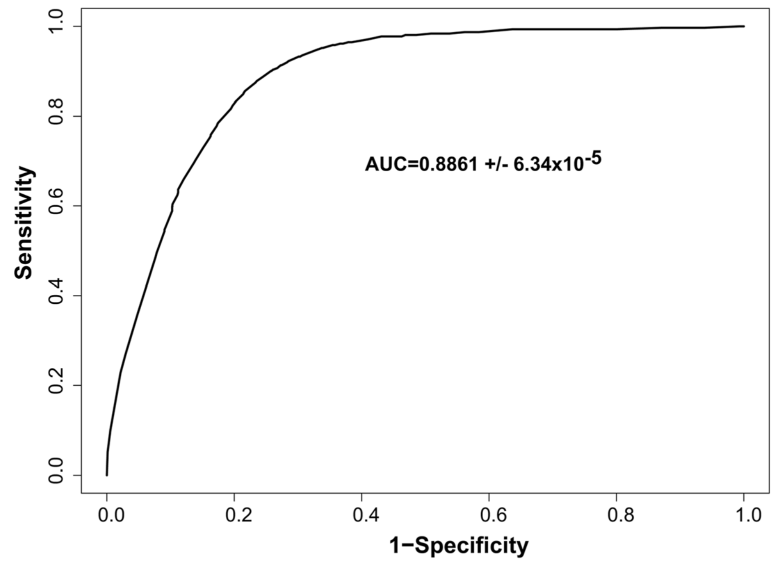

Fig. 3 ROC curve of the best generalized linear mixed model

of risk can be identified and associated with three different parts of Thailand (i.e., Northern, Central and Southern parts) and are related with the periods of flooding. The difference in these flooding periods is mainly due to two factors: a) the difference of rainfall seasonality between southern Thailand and the rest of the country, and b) the delay between rainfall and flooding between the central part and the northeastern part of the country. The central part of the country is downstream of the most important rivers in Thailand, and major flooding occurs later than in the rest of the country, in September to November, with an increased intensity. This explains why high risk occurs for most districts in this period, which also corresponds to its high population [12].

With the backward step approach, the final model includes human and livestock population densities. However, the model results show that those variables are not significant. Furthermore, these variables should be interpreted very cautiously because several confounding factors could be involved. Thus, they were kept because they improved the final model (based on the decrease of the AIC), but they should not be over-interpreted.

Our study was based on a cross-sectional survey [4], which was limited as there may be procedural concerns.

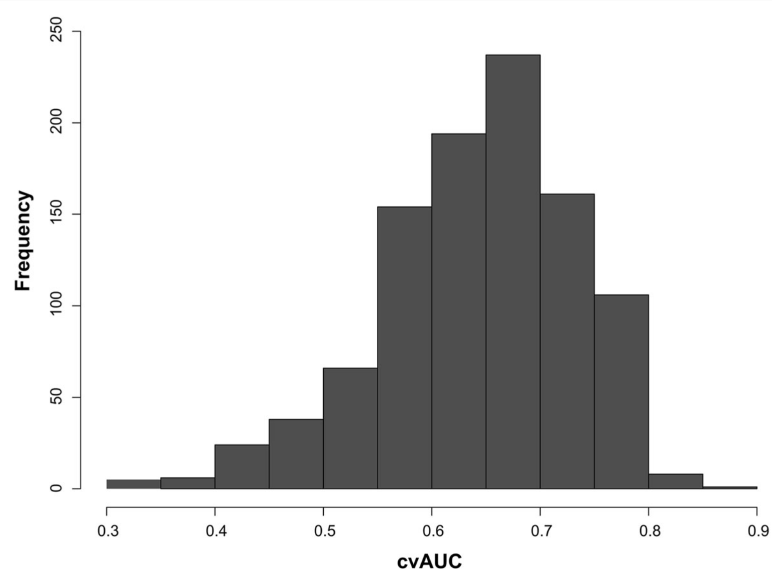

Fig. 4 The cross-validated AUC distribution

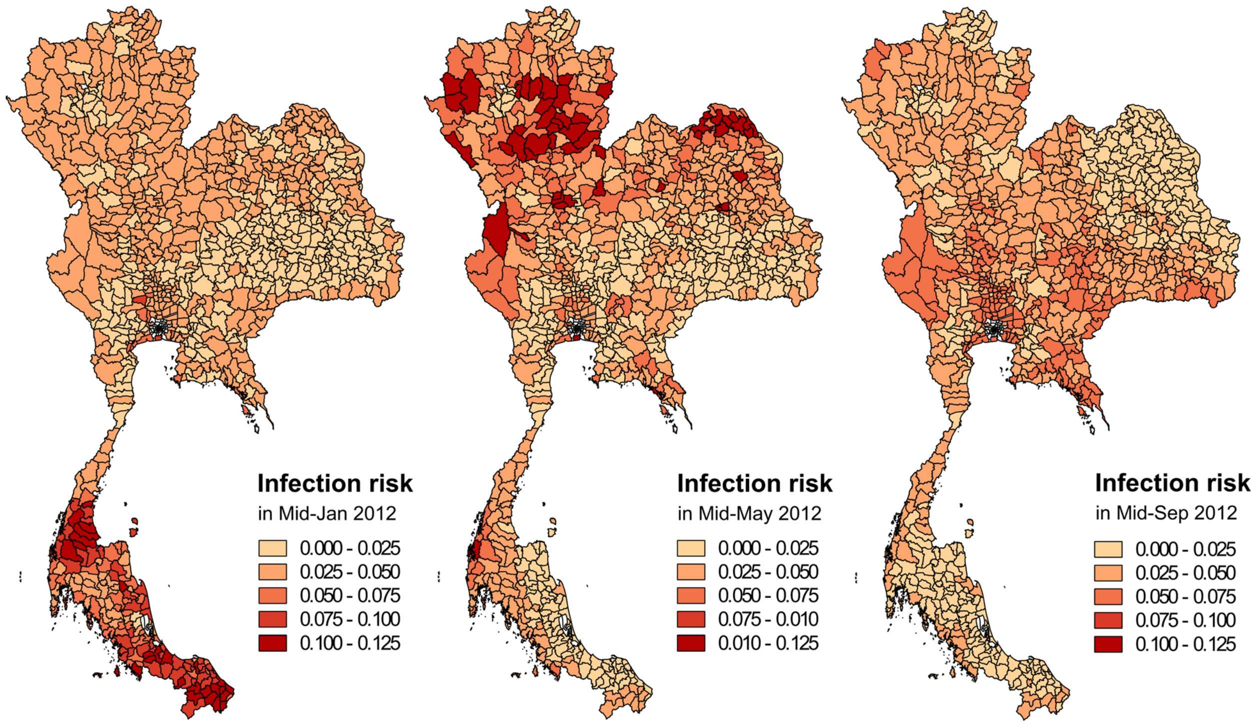

Fig. 5 Map of the prediction of leptospirosis infection risk using the final multivariate linear regression model in three different periods of 2012. A leptospirosis infection risk of 0.1 indicates that approximately 1/10 livestock are expected to be positive by LAMP for leptospirosis infection. The non-predicted districts are presented in white

It does not provide data for all districts in the country and for all seasons in each district. A longitudinal survey is strongly suggested in further studies, with repeated sampling in a larger number of districts in the whole country. It would provide better data to understand the seasonality of leptospirosis infection and could provide a more accurate disease transmission model. The samples in each district were mostly collected only once. However, the samples were distributed over every part of Thailand for all seasons. Furthermore, the model had a relatively good performance (AUC =0.8861) but a lower and quite variable cross-validated AUC (mean cvAUC = 0.6427, sd = 0.0827, Fig. 4). This difference between AUC and cvAUC, and the variability of the cvAUC may be explained by the relatively small size of our dataset at the district level leading to a small validation dataset (71 districts for the training dataset and only 36 for the validation dataset). Furthermore, given this size limit, some validation datasets may include a different proportion of southern districts than their matching training datasets. The difference of flooding patterns between southern Thailand and the rest of the country may then further explain the lower cvAUC. Training the model on a larger dataset and having an independent large dataset to validate it would help build a more robust model.

The presence of pathogenic leptospires in livestock was tested with LAMP [4, 10], which allows a simple and rapid diagnosis of leptospirosis with high accuracy. However, this technique cannot provide any genotypic information, thus could not be used to compare pathogenic strains in the study. However, in Thailand, the accuracy of LAMP (97.0%) was higher than real-time PCR (91.9%) [10]. Thus, results from this technique can be used with confidence in our study to investigate the association of livestock leptospirosis infection with environmental factors.

Other environmental risk factors such as soil type and land use, which were not explored in this study, may be required to better characterize leptospirosis infection risk. A previous study showed that agricultural land and clay loams soil are significantly associated with leptospirosis infection in humans [37]. These factors could influence the identification of high-risk areas and help improve our model.

Other individual variables such as sex and age of the animals investigated were not considered in this study due to data limits. These factors could help us to improve the model and may impact the results [38, 39]. *Leptospira* can infect a wide range of livestock including pigs, goats and sheep [40, 41]. Studies of these animals should also be implemented as they may also contribute to leptospirosis epidemics. However, the present study focused on the flooding indicator associated with cattle and buffalo infection. The good performance of the model shows that flooding is a major factor that should be considered in leptospirosis risk models.

Conclusion

Our findings could identify flooding as a major driver of the risk of leptospirosis infection in cattle and buffalo. Public awareness about the risk of leptospirosis during flooding should be raised in order for people to take prevention measures when possible. The risk maps could also help to develop effective intervention strategies and optimize the allocation of public health resources, veterinary care and control measures. A high level of livestock infection could increase the risk to human health due to contact with infected animals or a contaminated environment by the urine of infected animals [2, 34]. Livestock may then play an important role as a potential indicator of high-risk areas for leptospirosis in humans. Further study needs to be done to assess the risks associated with contact between livestock and humans. In this regard, further data needs to be collected and made available.

Additional files

Additional file 1: Table S1. Summary results of the univariable linear regression model (with binomial function and random effect). (DOCX 14 kb)

Additional file 2: Figure S1. Percentage of flood area in 2012. **Figure S2.** The monthly rainfall of Thailand in 2012. **Figure S3.** Prediction of leptospirosis infection risk in 2016. The non-predicted districts are
presented in white. **Figure S4.** Percentage of Flood area in 2016. **Figure S5.** Maps of human density (people/km^2) and livestock density (animal/km^2). (DOCX 3416 kb)

Abbreviations

AIC: Akaike Information Criterion; AUC: Area Under the Curve; GLMM: Generalized linear mixed model; LAMP: Loop-mediated isothermal amplification; MNDWI: Modified normalized difference water index; MODIS: Moderate Resolution Imaging Spectroradiometer; ROC: Receiver Operating Characteristic; SRTM: Shuttle Radar Topographic Mission; TRMM: Tropical Rainfall Measuring Mission

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Availability of data and materials

The data supporting the findings can be found in the main paper and in additional supporting files.

Authors' contributions

SC: conceptualized, participated in its design, performed the analysis, revising it critically for important content, wrote the first draft and wrote the manuscript. JC: conceptualized, participated in its design, analysis, revising it critically for important content, and wrote the manuscript. KCM: participated in its design, analysis and involved in drafting the manuscript. AW: involved in drafting the manuscript, participated in acquisition of data and revising it critically for important content. DS SC JC: participated in data extraction and interpretation. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The need for approval was waived as this study used published animal data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Modelling Leptospirosis transmission in Thailand: accessing the impact of flooding and weather conditions

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Abstract

The epidemic of leptospirosis in humans continues to this day, causing incidences annually in Thailand. We developed a mathematical model to study the transmission dynamics between humans, animals, and a contaminated environment. We compared different models that included the impact of flooding and weather conditions on the transmission rate from a contaminated environment, the leptospire shedding rate and the multiplication rate of the leptospires in the environment. We found that the model with the transmission rate dependent on flooding and temperature best-fit the reported human data on leptospirosis in Thailand. Our results highlight that flooding indicators have the most impact on transmission, indicating a high degree of flooding leads to higher cases. Sensitivity analysis showed that the transmission of leptospires from the contaminated environment was the most important parameter for the total number of human cases. Our results suggest that public health policy makers should guide the people who work close to, or in contaminated environments to avoiding potential sources of leptospirosis, or by protecting themselves by wearing boots to reduce the leptospirosis outbreak.

Keywords: Leptospirosis, transmission dynamics, Flooding, Weather conditions

Introduction

Leptospirosis is a worldwide zoonotic bacterial disease, that is particularly endemic in tropical and subtropical countries[1,2]. The infection of humans is mainly caused by direct contact with an infected animals and also by indirect contact with urine of infected animals through cuts in the skin or mucous membranes in a contaminated environment[1,3].

In humans, the epidemic of leptospirosis continues to this day, causing incidences annually. The highest number of cases reported in Thailand is during the rainy season in mid-May to mid-October[4]. High-risk groups include farmers and other agricultural workers, who are likely to come into contact with infected animals, and contaminated wet soil and water during their daily activities[5-7]. In addition, leptospirosis in livestock is also considered an important disease, causing reproductive failures (such as abortion, embryonic death, stillbirths, and weak off-spring), decreased milk production and growth rates[8-11]. A relatively high prevalence of leptospirosis has been detected in the urine of cattle and buffalo in Thailand[8]. Contact with infected livestock during production was also investigated, and was found to increase the risk of infection[12]. This spirochete bacteria are mainly transmitted through injured or cut skin in contact with contaminated water or soil. Leptospires may survive from a few weeks to almost a year in surface water or wet soil even during dry days[13].

Most of the previous leptospirosis models focused on spreading of the disease in humans and rodents[14-16]. However, compartment models of leptospirosis, with links between the host or livestock and the environment, have also been proposed. Babylon *et al*. presented a simple Susceptible-Infective (SI) model to describe the spreading of leptospirosis in lambs in contact with free-living leptsopires[17]. A model to study the leptospire infection dynamics in Norway rat (*Rattus norvegicus*) as the reservoir host in the environment was also presented[18]. However, the model should be composed of human, animals and environmental compartments for leptospirosis infection dynamics. Baca-Carrasco *et al*. presented an SI model to study the transmission in humans and animals and included bacteria in the environment[19]. The direct transmission between animals and humans has also been explored[20].

Thus far, those mathematical models did not consider seasonal effects, flooding or weather conditions. Seasonal and weather conditions have been shown to be associated with an increased leptospirosis risk[12,21-24]. In this work, we propose different leptospirosis transmission models, which considers the impact of environmental factors such as seasonal flooding, and weather conditions. The livestock species, *i.e.*, buffalo, cattle, goats, pigs, and sheep, are the animal reservoirs and contribute to the circulation of leptospirosis in humans and the environment[25,26]. The reported data on human leptospirosis in Thailand was used to fit the transmission models to help identify the factors that influence the leptospirosis transmission dynamics. The proposed transmission models may help to understand the processes of leptospirosis transmission in Thailand and allow more accurate predictions of future outbreaks and better control of the disease.

Methods

Data

In this study, reported cases of human leptospirosis were retrieved from the national disease surveillance (report 506), Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand[27]. Most positive cases were suspected leptospirosis cases, based on the clinical diagnosis made by attending physicians. The clinical criteria for leptospirosis were high fever, chills, headache, with at least one of the following symptoms including abdominal pain, red eyes, neurological symptoms (such as stiffness, abnormal feelings, etc.), and dry cough or cough with bloody sputum, and a career history of exposure to water areas or environments contaminated with animal excreta[28]. Some of the suspected cases were then examined using laboratory tests such as Latex agglutination test (LA), Dipstick test, Lateral flow test, Microcapsule agglutination test (MCAT), Immunofluorescent antibody test (IFA), Microscopic agglutination test (MAT) or ELISA for confirmation. The suspected cases were mainly reported from public hospitals with a small fraction from private hospitals. In this research, we analyzed all reported cases from 2010 to 2016 in two provinces (*i.e.*, Si Sa Ket and Surin), in which the highest number of cases were reported.

Data collection was performed as a part of routine clinical examination procedures of the Thai Ministry of Public Health surveillance and response. Data collection was approved by the Ethics Committee of the Ministry of Public Health of Thailand. Data containing the patient's medical records, without any patient information except location, were de-identified prior to analysis.

The remotely sensed environmental data obtained included the modified normalized difference water index (MNDWI) and the Land Surface Temperature (LST). MNDWI was extracted from the data of the Moderate Resolution Imaging Spectroradiometer (MODIS) of the Terra satellite (Surface Reflectance 8-Day L3 Global 500m SIN Grid V005 (MOD09A1)). We used band 4 (green) and band 7 (infrared) to calculate the Modified Normalized Difference Water Index (MNDWI)[29,30]. Within all provinces, each pixel was classified as flood area if the MNDWI value was greater than or equal to zero[21,30]. Permanent water bodies were masked out using QGIS version 2.8.3[31]. The number of flooded pixels was counted to calculate the index of land flooding, which was then used to calculate the percentage of area flooded.

The LST was extracted from the MODIS Terra product (MOD11A2) with Emissivity 8-Day L3 Global 1 km, which is composed of the daily LST product (MOD11A1) with a 1 km resolution and stored on a 1 km Sinusoidal grid as the average values of clear-sky LSTs during an 8-day period[32].

The amount of rainfall was obtained from the real-time Tropical Rainfall Measuring Mission (TRMM) Multi-Satellite Precipitation Analysis (TMPA-RT)[33]. We derived daily precipitation and daily accumulated precipitation from the TMPA product: 3B42RT[34,35].

The initial human population data were obtained from the WorldPop database, which presents the number of people per pixel (http://www.worldpop.org.uk). The initial livestock population of each specie (buffalo, cattle, goat, pigs, and sheep) was obtained from the Information and Communication Technology Center (ICT), Department of Livestock Development of Thailand at the province level (http://ict.dld.go.th).

Model for leptospirosis transmission

A simple SIR model of two groups is used to study the transmission dynamics of leptospirosis between humans, livestock and the contaminated environment. Susceptible human and livestock individuals are introduced, denoted by S_h and S_a, respectively. S_h and S_a can become infected through contact with infected livestock and/or the contaminated environment. The infected livestock can shed leptospires into the environment and increase the number of leptospires (L compartment) in that province. The hygienic level of the contaminated environment can be defined as the density of leptospires. The leptospires die at a rate μ_L. Infected humans and animals recover at the constant rates γ_h and γ_a, and loss immunity at the rates ν_h and ν_a, respectively. Both population sizes are assumed to be constant. In this work, we developed the transmission model based on previous studies[19,20]. The leptospirosis transmission model is described by the following set of differential equations:

$$
\begin{aligned}
\frac{dS_h(t)}{dt} &= \mu_h N_h - \beta_{ha}(t)\frac{S_h(t)I_a(t)}{N_h} - \beta_{hL}(t)h(t)\frac{S_h(t)}{N_h} + \nu_h R_h(t) - \mu_h S_h(t),\\
\frac{dI_h(t)}{dt} &= \beta_{ha}(t)\frac{S_h(t)I_a(t)}{N_h} + \beta_{hL}(t)h(t)\frac{S_h(t)}{N_h} - \gamma_h I_h(t) - \mu_h I_h(t),\\
\frac{dR_h(t)}{dt} &= \gamma_h I_h(t) - \nu_h R_h(t) - \mu_h R_h(t),\\
\frac{dS_a(t)}{dt} &= \mu_a N_a - \beta_{aa}(t)\frac{S_a(t)I_a(t)}{N_a(t)} - \beta_{aL}(t)h(t)\frac{S_a(t)}{N_a(t)} + \nu_a R_a(t) - \mu_a S_a(t), \qquad (1)\\
\frac{dI_a(t)}{dt} &= \beta_{aa}(t)\frac{S_a(t)I_a(t)}{N_a(t)} + \beta_{aL}(t)h(t)\frac{S_a(t)}{N_a(t)} - \gamma_a I_a(t) - \mu_a I_a(t),\\
\frac{dR_a(t)}{dt} &= \gamma_a I_a(t) - \nu_a R_a(t) - \mu_a R_a(t),\\
\frac{dL(t)}{dt} &= \omega(t)I_a(t) + m(t)g(t)L(t) - \mu_L L(t),
\end{aligned}
$$

where $N = S + I + R$ for livestock and human compartments.

In our model, we assumed that, as a zoonosis disease, the human-human transmission does not exist[10]; thus infection in humans always developed from animal sources or the contaminated environment. The leptospires shedding from humans into the environment is neglected in our study as the likelihood is very low. The function $g(t) = \frac{\chi - L(t)}{\chi}$ in equation (1) represents the logistic growth multiplier, which allows the growth to depend on the current number of leptospires and limits excessive growth, where χ is the maximum carrying capacity, or saturating population size. A saturation term, $h(t) = \frac{L(t)}{L(t)+\kappa}$, is added to limit the effect of transmission due to the large number of leptospires[14,36], where κ is the density of leptospires in the environment at which the transmission rate is $0.5\beta_L(t)$. The diagram of the model and its relationship between the compartments is provided in Fig. 1. A set of parameters is shown in Table 1.

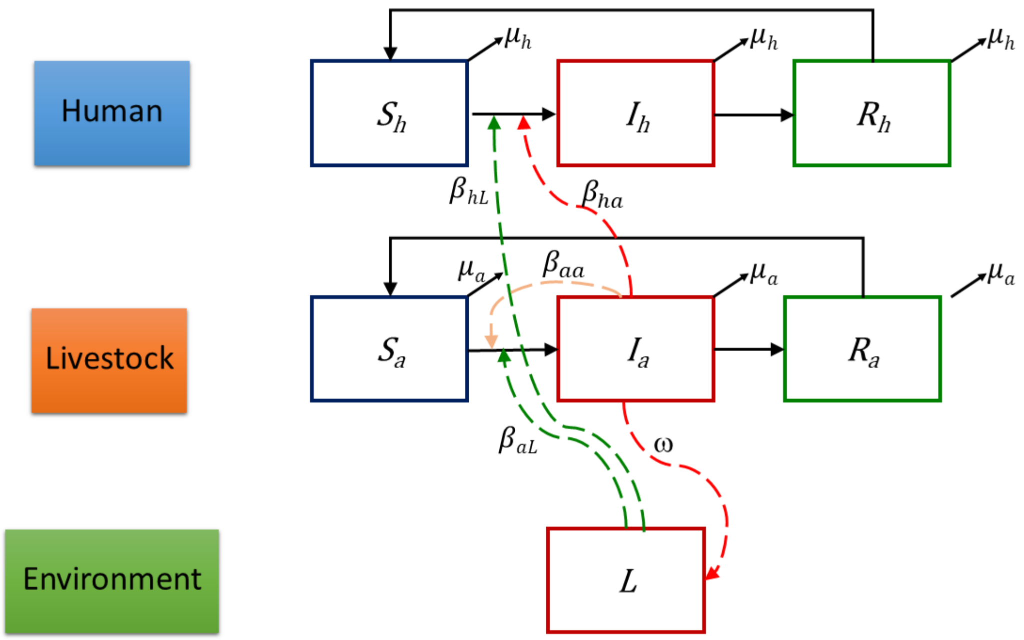

Figure 1. Dynamics of leptospirosis spread between humans, livestock and the contaminated environment. Dashed green arrow shows the transmission route from the contaminated environment to susceptible livestock (S_a) and humans (S_h). Infected livestock (I_h) transmit leptospires to humans and shed to environment (red dashed line) and to livestock (orange dashed line).

Table 1: A set of parameters.

Description	**Symbol**	**Values**
Birth and death rate of humans	$1/\mu^h$	70 years (estimated)
Duration of infection for humans	$1/\gamma^h$	14 days (estimated from[3])
Duration of loss of immunity for humans	$1/\nu^h$	720 days (estimated from[3])
Transmission rate from infected livestock to human	β_{ha}	fitted
Birth and death rate of livestock	$1/\mu^a$	3 years (estimated)
Duration of infection for livestock	$1/\gamma^a$	200 days (estimated from[37])
Duration of loss of immunity for livestock	$1/\nu^a$	540 days (estimated)
Transmission rate from infected livestock to livestock	β_{aa}	fitted

Duration of contamination for the environment	μ_L	0.02381 day^{-1} (estimated from[36])
Density of leptospires at which the transmission rate from the environment is $0.5\beta_L(t)$	κ	10^2 km^{-2} (estimated from[36])
Maximum carrying capacity	χ	1x10^5 (estimated)
Density of the free living leptospires in a province at $t = 0$	$L_i(0)$	10^{-3} km^{-2} (estimated from[36])
Density of leptospires shed per infected livestock	ω	fitted
Transmission rate from the contaminated environment to human and livestock	β_{hL} and β_{aL}	fitted
Multiplication rate of the leptospires in the environment	m	fitted

Some of the parameters in equation (1) may be affected by flooding and weather conditions. In this work, we look at how these conditions can affect the transmission from the contaminated environment, leptospire shedding rate, and the multiplication rate.

The most important parameters are the transmission modes from the contaminated environment to susceptible humans and susceptible livestock (β_{hL} and β_{aL}). We hypothesized that the environment could influence the transmission of leptospirosis. Thus, the transmission terms are constructed as a linear function of normalized data of the percentage of flooded area ($f(t)$), total monthly rainfall ($\rho(t)$), and average monthly temperature ($T(t)$). The virulence of leptospires depends on temperature[38], leading to the inclusion of the average temperature, which may impact the transmission model. We examined four forms of transmission rate dependency corresponding to three environmental variables to test different hypotheses. These four transmission rates assumed the rates were linearly proportional to the environmental variable and are as follows:

(1) Flooding (M1-F): The transmission rates are given by:

$$\beta_{hL}(t) = h_1\big(1 + h_2 f(t - \tau_1)\big)$$

$$\beta_{aL}(t) = a_2\big(1 + a_2 f(t - \tau_1)\big)$$

(2) Rainfall (M1-R): The transmission rates are given by:

$$\beta_{hL}(t) = h_1\big(1 + h_2\rho(t-\tau_1)\big)$$

$$\beta_{aL}(t) = a_1\big(1 + a_2\rho(t-\tau_1)\big)$$

(3) Flooding and temperature (M1-FT): The transmission rates are given by:

$$\beta_{hL}(t) = h_1(1 + h_2 f(t-\tau_1) + h_3 T(t-\tau_2))$$

$$\beta_{aL}(t) = a_1(1 + a_2 f(t-\tau_1) + a_3 T(t-\tau_2))$$

(4) Rainfall and temperature (M1-RT): The transmission rates are given by:

$$\beta_{hL}(t) = h_1(1 + h_2\rho(t-\tau_1) + h_3 T(t-\tau_2))$$

$$\beta_{aL}(t) = a_1(1 + a_2\rho(t-\tau_1) + a_3 T(t-\tau_2))$$

where h_i and a_i are constant values (that were fitted) of each function for each transmission rate, and τ_1 and τ_2 are time lags, varying from 0-8 weeks, which are associated with the infection of humans.

The second model (M2-F and M2-R) are the leptospire shedding rate (ω), which is affected by rainfall. Infected livestock shed leptospires into the environment, which will then be a source of exposure for susceptible humans and livestock. The shedding rate can be described as a logistic curve, to limit its effect at high concentrations.

$$\omega(t) = \omega_0\left(\frac{\rho(t-\tau_1)}{\delta+\rho(t-\tau_1)}\right) \text{ and } \omega(t) = \omega_0\left(\frac{f(t-\tau_1)}{\delta+f(t-\tau_1)}\right)$$

where δ is an inferred threshold parameter corresponding to the rate of half of the maximum shedding rate due to rainfall or the effect of flooding.

The last model affects the multiplication rate of the leptospires in the environment (m), which depends on three environmental variables, namely, the percentage of flooding area ($f(t)$), total monthly rainfall ($\rho(t)$) and average monthly temperature ($T(t)$). The multiplication rate is given by:

(1) Flooding (M3-F): $m(t) = x_1(1 + x_2 f(t-\tau_1))$

(2) Rainfall (M3-R): $m(t) = x_1(1 + x_2\rho(t-\tau_1))$

(3) Flooding and temperature (M3-FT): $m(t) = x_1(1 + x_2 f(t-\tau_1) + x_3 T(t-\tau_2))$

(4) Rainfall and temperature (M3-RT): $m(t) = x_1(1 + x_2\rho(t-\tau_1) + x_3 T(t-\tau_2))$

where x_1, x_2 and x_3 are constant values (fitted parameters).

Ten models (M1-F, M1-R, M1-FT, M1-RT, M2-F, M2-R, M3-F, M3-R, M3-FT and M3-RT) were considered individually and compared to the null hypothesis, where all parameters are constant values. The effect of flooding was compared to the effect of rainfall without and with a temperature effect. The combined models that use multiple effects above were also considered. A stochastic simulation approach was employed using a tau-leaping algorithm with a fixed time step[39]. Using the parameters of the best model, 1,000 simulations were generated.

Parameter estimation and sensitivity analysis

To estimate the parameters of our model, we assumed that the epidemic was initiated by free-living leptospires in that area by setting the initial number of free-living leptospires to a low concentration (Table 1). We linked the biweekly human cases from the simulation results with the corresponding actual reported human cases from 2010 to 2015. The best fit was obtained by maximizing a normal log-likelihood estimation, which produced simulation results that were most similar to the reported data. We used the nlminb function in R, which is a quasi-Newton method with a constrained bound, to find the optimal set of parameters[40]. The model that shows the minimum negative log-likelihood was selected as the best model.

In this work, according to previous findings, we considered the effect of time lag (τ) on the environmental data to leptospirosis cases due to transmission. Rainfall has been observed to be associated with leptospirosis, often with a time lag of 1-3 months[41,42]. We set the maximum time lags of flooding and rainfall to be eight weeks. We set the lag period to be the same for the effects of temperature, raining, and flooding in this model[24].

To perform a sensitivity analysis of which parameters influence the effect of leptospirosis transmission the most, we used the Partial Rank Correlation Coefficients (PRCC) technique[43,44]. Then, we used the Latin hypercube sampling(LHS), which is a statistical Monte Carlo sampling technique, to sample the parameters using the lhs package in R[45]. 1,000 parameter sets were sampled with each parameter sampled from a uniform distribution. The PRCC was ranked as a response function to the cumulative new cases in each province using the sensitivity package in R with bootstrapping 1,000 times to obtain a 95% confidence intervals[46]. Based on the linear assumption, positive (negative) PRCC values imply positive (negative) correlations to the response function.

Estimation of time-dependent reproduction number (R_{td})

The basic reproductive number (R_0) is generally defined as the average number of secondary infected individuals caused by an infected individual in a population that is completely susceptible. Due to the complexity of the model and the time-dependent variables, there is no exact way to explain R_0 for this model, as it is a complex function of many different variables. An alternative method, proposed by Wallinga *et al*[47], computes the reproduction number from the observed cases using a likelihood-based method, calculated by averaging the overall transmission networks which makes it fit an epidemic curve[48]. In this work, we calculated a time-dependent reproduction number (R_{td}) according to the R0 package in R[48]. The number of biweekly cases obtained from the simulations of the best model in three provinces was used to estimate R_{td}. The serial interval between successive infections of the reported epidemic was identified and used to estimate the generation time distribution, with the mean and standard deviation (sd) of each province, using the R0 package. Then the R_{td} of each province was estimated with the 95% confidence interval.

Results

Based on the annual reports of leptospirosis cases in Thailand from 2010 to 2016, it appears that the disease continues to spread throughout the country (Fig. 2(A)). The highest number of annual cases was observed mostly in the northeastern region, which also had the highest number of cumulative cases (Fig. 2(B)). In this work, we considered two provinces, namely, Si Sa Ket (highest number of cumulative cases) and Surin (second highest number of cumulative cases) for testing the models. The time series of reported biweekly cases were plotted with the percentage of flooding, the amount of rainfall, and temperature (Fig. S1.). We found that the time series of biweekly reported cases in the two provinces showed a similar trend. The percentage of flooding and the amount of rainfall were found to increase around the same time of year when the number of reported cases increased. However, the temperature was negatively correlated with incident cases.

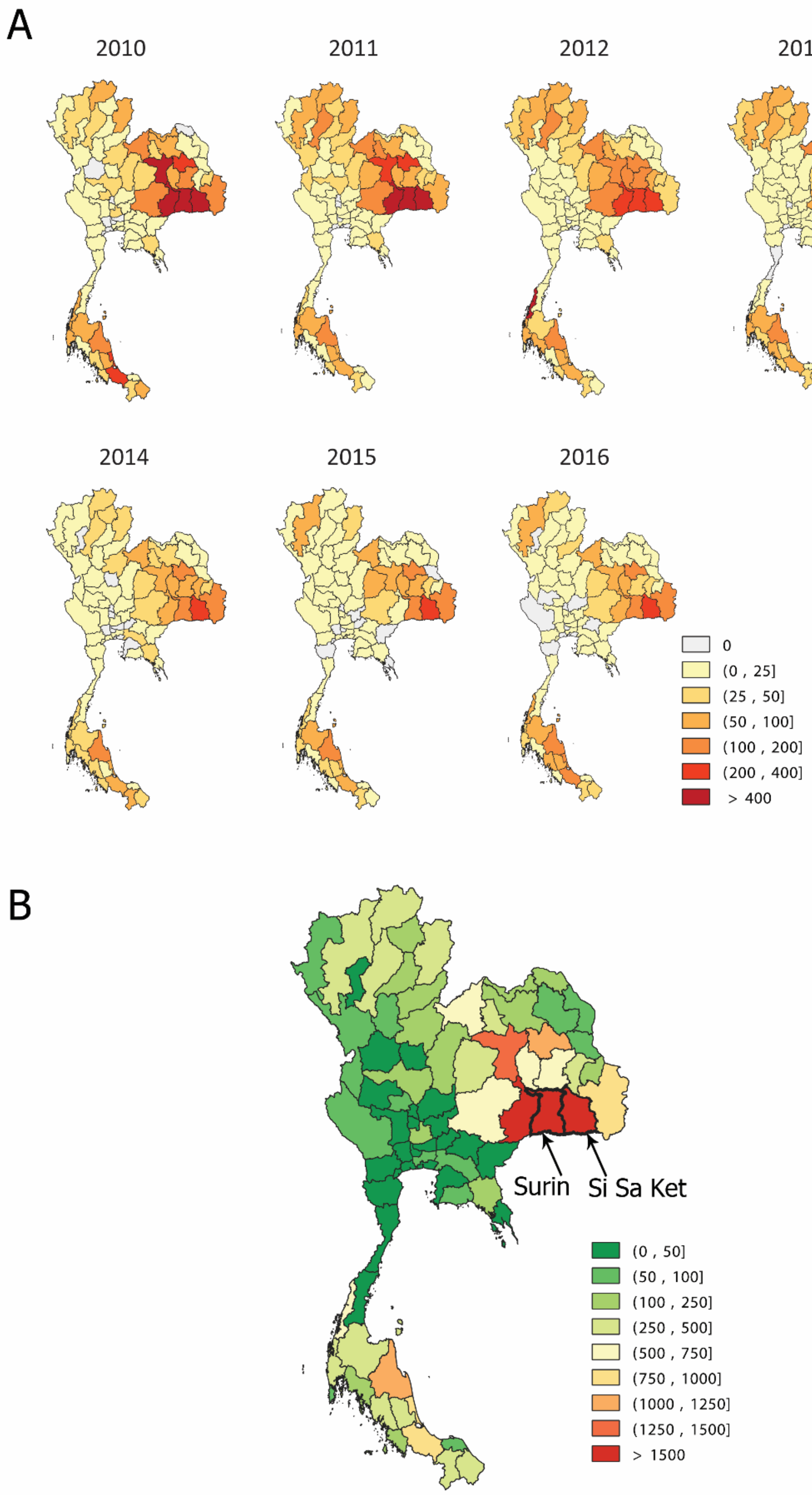

Figure 2. The map of reported cases in Thailand. The annual reported cases during 2010-2016 (A). The total reported cases during 2010-2016 (B).

Using the model described in the methods section, we fit eleven models (our ten models plus the null model) to the reported cases from 2010 to 2015 with time lags between 0-8 weeks for each province (Fig. 3). In general, we found that model 1 (M1) improved the fit, which indicated that making the transmission rate a linear function with environmental variables has an important impact on the infection dynamics in humans. Comparing the models incorporating flooding or rainfall factors (M1-F and M1-R), we found the model including the flooding factor fit better. The models that also included a temperature effect showed better performance. Overall, the model with the transmission rate dependent on flooding and temperature (M1-FT) had the lowest negative log-likelihood. Thus, we selected the M1-FT as the best-fit model for further analysis. The log-likelihood value of M1-FT varied time lags of flooding showed a similar pattern, which has a high value for time lag around one month (Fig. S2.). The effect of time lag on the temperature was found to be different than the time lag associated with flooding. The results indicate that the transmission dynamics depend on the weather in the given areas.

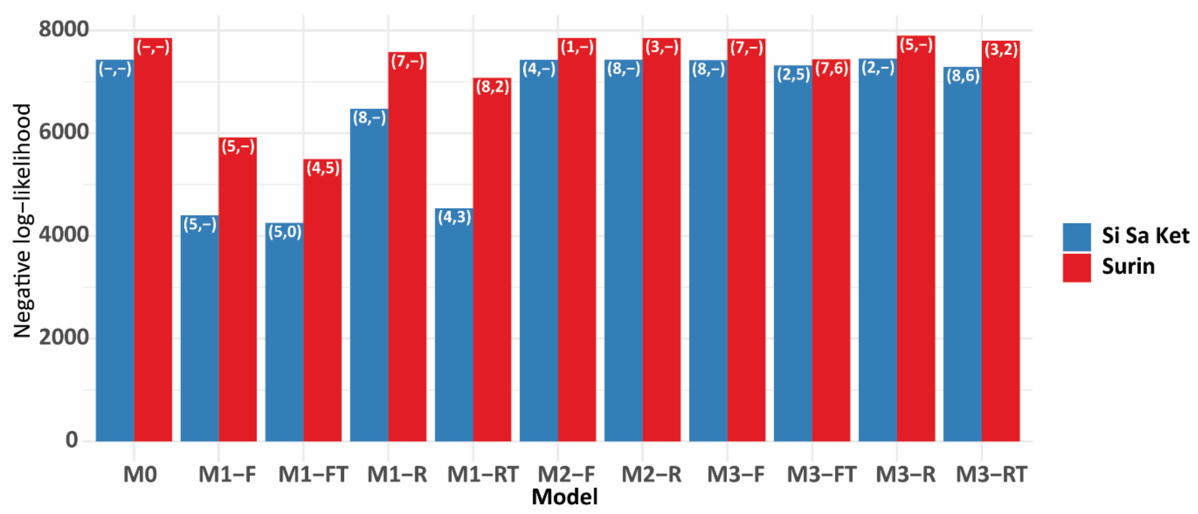

Figure 3. Bar chart of negative log-likelihood values for the ten models compared to a null model (M0) for the two provinces. The parentheses of each bar shows the time lag in week of flooding (rainfall) and temperature (t_1, t_2).

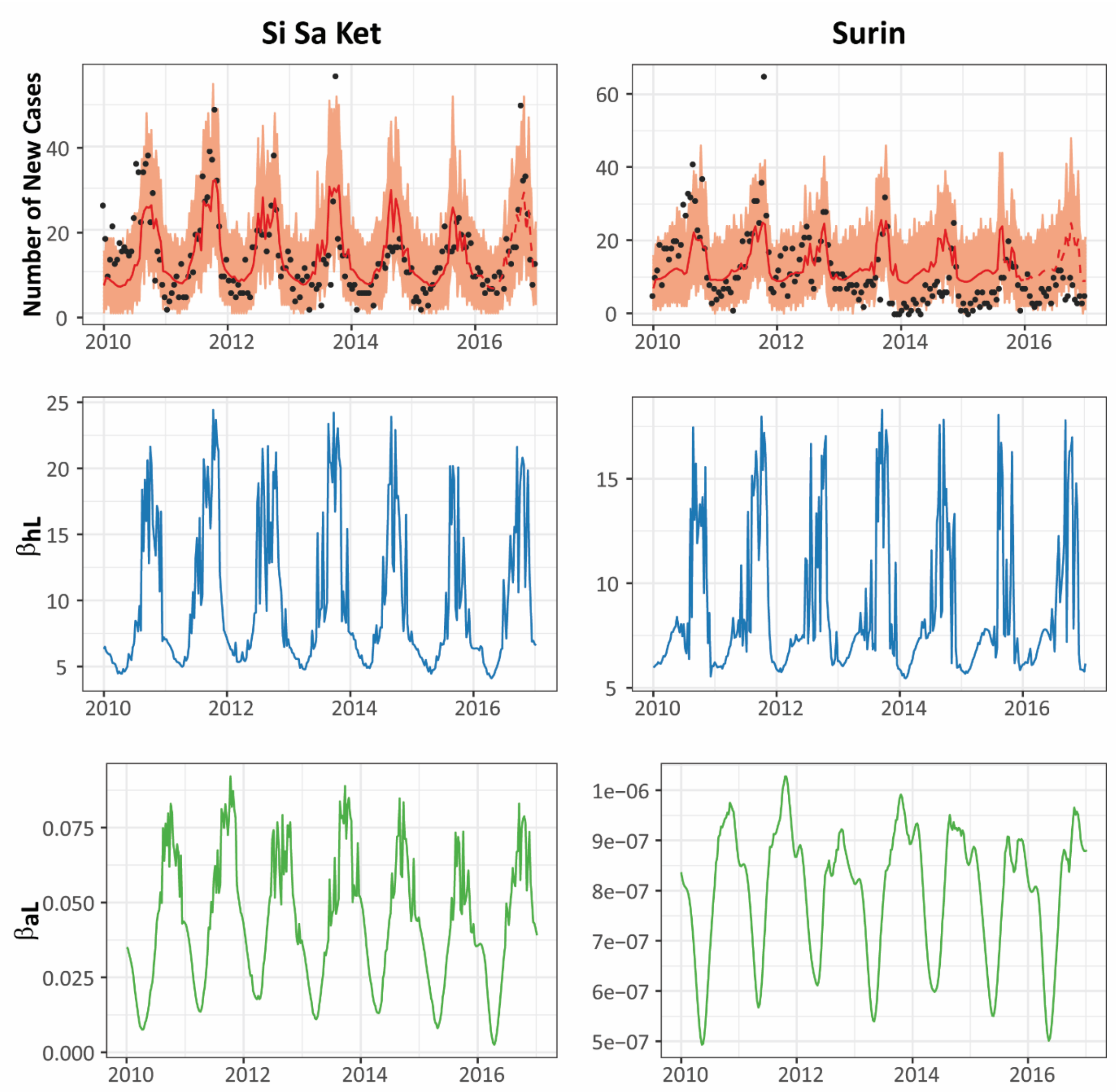

Figure 4. The fitted results of the M1-FT model (red line) compared to the reported cases of leptospirosis (black dot). The orange shaded area displays 1,000 curves of the stochastic simulations. The red dashed line represents the predicted cases for 2016. The time-dependent transmission rate from the contaminated environment to susceptible human and susceptible livestock (β_{hL} and β_{aL}) correspond to values in Table S1 are shown in the blue and green lines, respectively.

The M1-FT fitting and the stochastic simulation results, using the parameters shown in Table S1, are shown in Fig. 4. The stochastic output captures well the reported data. These results provide a reasonable fit with the predicted cases for 2016. Our model can provide more understanding on the transmission dynamics in contaminated environments.

The transmission rate from the contaminated environment to humans and livestock is plotted versus time according to the flooding and temperature factors (Fig. 4). The average transmission rate from the contaminated environment to humans (β_{hL}) over time is 9.886 and 8.737 for Si Sa Ket and Surin. This corresponds to a decline in the total number of reported cases during the dry season. The transmission rate from the contaminated environment to livestock (β_{aL}) also varied with time. It was higher in Si Sa Ket and lower in Surin. However, the β_{hL} was always the highest transmission rate. This result indicated that the main reason for human infection is due to the transmission of leptospires from the contaminated environment, rather than from contact with infected animals. Comparing the coefficients of β_{hL}, the flooding indicator had the most impact on transmission, which indicates a high amount of flooded area leads to higher cases.

The fitting results indicate that our model is capable to reproduce the incidences of the leptospirosis epidemic, using the seasonal changes of the amount of flooded area as an indicator of increased infection rates. The number of new infection cases can be predicted during winter, depending on the parameters calculated in the given areas.

In this work, we estimated the time-dependent reproduction number (R_{td}) for two provinces with the 95% confidence interval using the simulation results as shown in Fig. 5. We found the R_{td} oscillated around 1.0 which suggests it is an endemic disease, as expected for leptospirosis in Thailand. The mean (sd) of R_{td} is estimated at 1.020 (0.198) and 1.011 (0.158) for Si Sa Ket and Surin. A similar pattern of R_{td} was observed for both provinces in the same region in the simulated cases. Note that this estimation was based on the observed human cases. Normally, leptospirosis has a basic reproduction number close to zero due to its minimal transmissibility among human population. However, this estimation could provide a better picture of how leptospirosis transmits from animal sources and contaminated environments to humans.

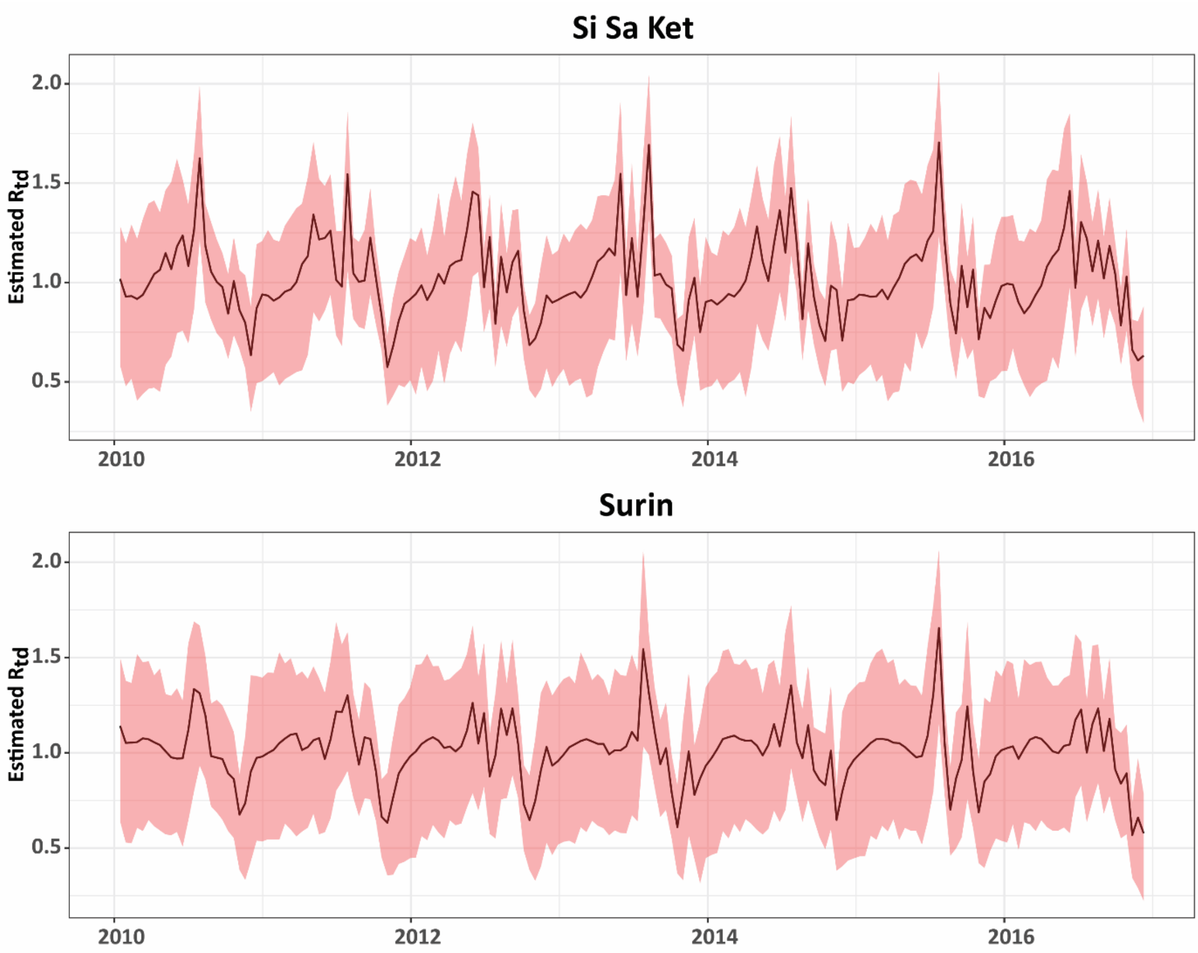

Figure 5. The estimated R_{td} for the two provinces plotted with the 95% confidence interval.

As no vaccine or specific medicines are available for leptospirosis, the most important strategy to control the disease is to decrease the transmission rate. Figure 6 shows the PRCC values with 95% CI, obtained for the ten parameters in Table S1. Absolute PRCC values greater than 0.3 are considered important parameters. We found that the parameters of β_{hL} (h_1, h_2 and h_3) were the most important on the total number of cases for all provinces. Our results also suggest how decreasing the transmission rate of leptospirosis from the contaminated environment to human can affect the leptospirosis dynamics to reduce the number of human cases. Figure 7 shows how the number of human cases can be reduced as the transmission rate of β_{hL} is reduced. A 90% reduction ($0.9\beta_{hL}$) could reduce the total number of human cases by about 90%. Considering the overall results, this study suggests that we should avoid contacting contaminated environments during flooding.

The infection rate extrapolated from the parameters of Si Sa Ket were also calculated for 2016 in other providences of Thailand (Fig. S3.). Interestingly, we found that high infection rates were predicted in other regions rather than just the northeast. This may due to the high percentage of flooded areas observed in the other regions. Our results also suggest that the public health sector should increase awareness of outbreaks in these regions.

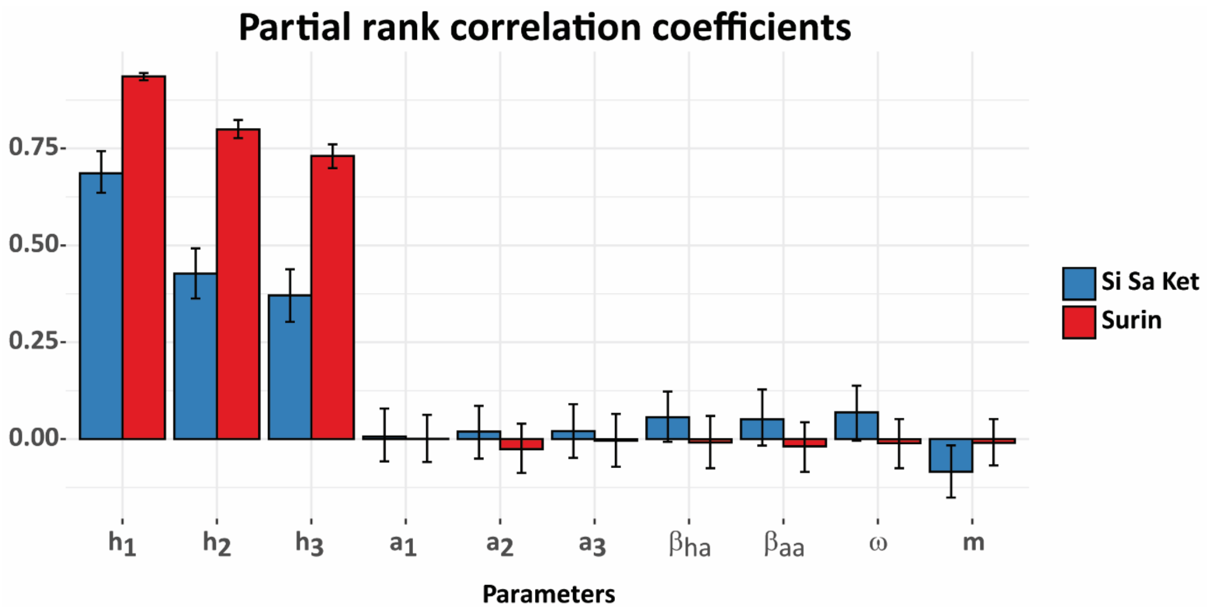

Figure 6. Partial rank correlation coefficients of the ten parameters and the total number of cases, plotted with an error bar showing the 95 % confidence interval. The h_i and a_i are constant values to calculate the transmission rates β_{hL} and β_{aL}, respectively.

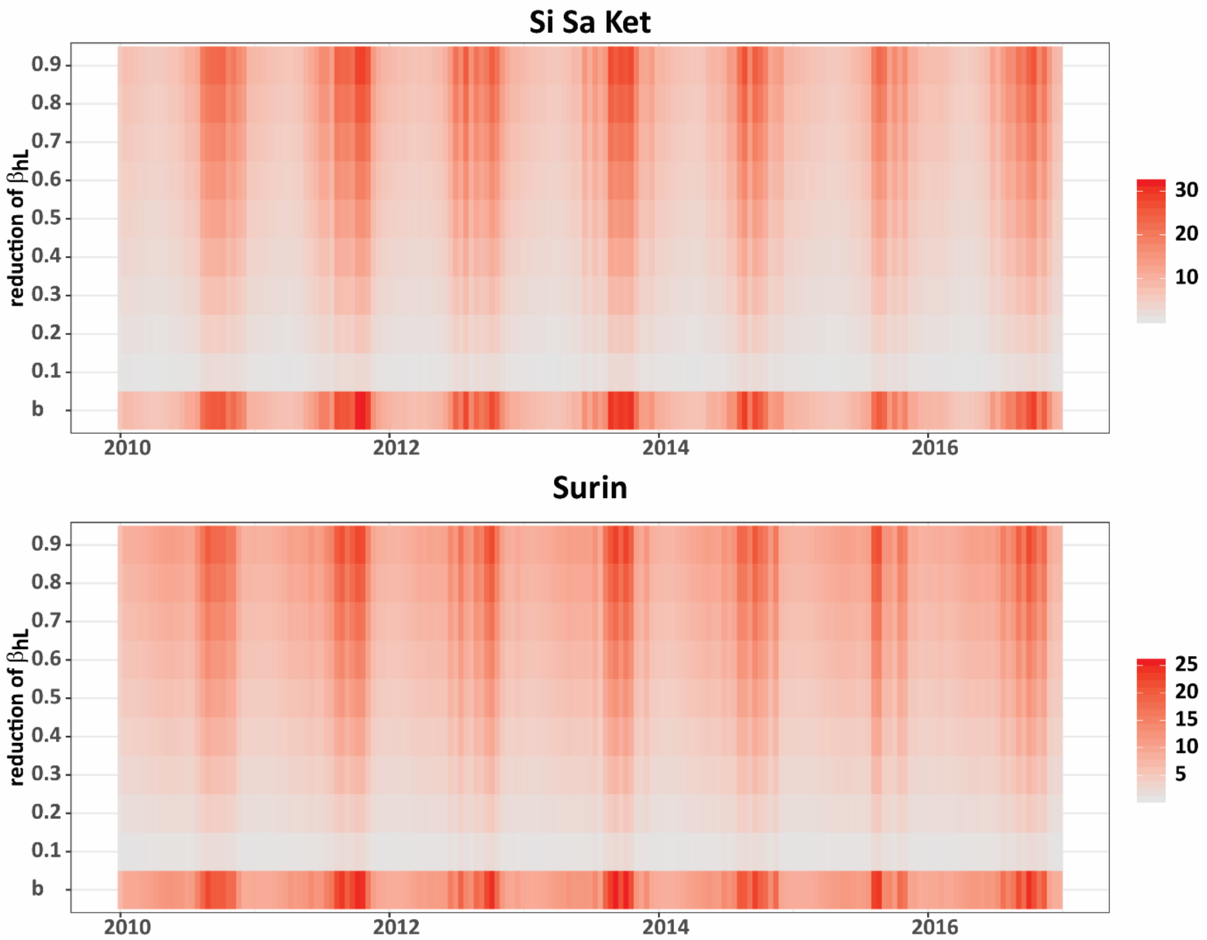

Figure 7. The number of human cases as the transmission rate from the contaminated environment to human (β_{hL}) of M1-FT is varied between $0.1\beta_{hL}$ to $0.9\beta_{hL}$, where b is the baseline.

Discussion

In this work, dynamical models, that include environmental data are presented and used to describe the transmission of leptospirosis in two provinces in the northeastern region of Thailand. This work presents the first attempt to incorporate environmental data into the mathematical models of leptospirosis transmission. The annual change of the environmental data can describe the seasonal epidemic with higher prevalence during the rainy season for the northeastern region, than a model not incorporating any environmental data.

Our finding suggests that transmission from a contaminated environment, as opposed direct contact with an infected animal, is the best model. This study is novel by finding that the amount of flooded area in a region, which obtained from a remotely sensed data, is the most important factor for leptospirosis transmission to humans. This implies that including a leptospires compartment, which refers to the number of pathogenic bacteria in the contaminated environment, reasonable describes the infection of humans during an endemic.

Previous studies have pointed out that leptospires survive and persist in the environment, both water and soil, for several weeks[49]. Environmental survival of pathogens can be an important parameter in epidemiology. During heavy rain with increased flooded areas, leptospires in the environment have more chances to enter the human body via cut skin. Working or living in flooded areas has been identified as a significant factor for increasing the contraction of leptospirosis[50]. Analysing our model, after fitting to human data from 2010-2015, the amount of flooded area was shown to be more important to improve the model as compared to the rainfall. Our results are consistent with a previous study that observed animals in Thailand from 2011–2013[21]. This indicates that flooding is a factor that influences the epidemiology of leptospirosis in both humans and animals. Flooding was also observed to be an important risk factor in other countries such as Argentina[51], Brazil[52] and Malaysia[53]. In our study, including the effect of temperature in the model improved the transmission model a modest amount. The temperature may affect leptospire virulence[38], and the transmission rate. The temperature effect observed in our study is in line with previous studies[54-56].

In this study, the time-dependent reproductive number was estimated for leptospirosis in humans. Normally, the basic reproductive number (R_0) cannot be estimated in humans due to minimal transmission between humans. However, in our case, we focused on how the transmission occurred in humans in term of R_{td}. Our model's estimation highlights that leptospirosis occurs mainly during mid-year for provinces in northeastern region.

From the PRCC analysis of our model, the transmission rate of leptospires to humans is most effected by the total number of cases. A disease control method, according to the PRCC results, suggest avoiding flooded areas, to reduce the transmission rate during an outbreak[57]. And protective equipment, such as wearing boots or gloves, is recommended when in contact with flooded areas.

Note that our proposed model is based on several assumptions, one of which is that the environmental parameters linearly affect the rates in the mathematical model. We do not consider other functions such as a Gaussian function due to the complexity. In general, models assume that the entire population is homogeneously mixed. The stochastic simulations in our results can estimate the fluctuations of the epidemic curve. Other animal, such as rodents, were not included due to the limitation of data on the rodent population. Rodents also carrying leptospires during the rainy period, and risk transferring the disease to humans[58]. Other factors such as human mobility, personal hygiene, and protective equipment, were also not accounted for in this study. The fitting process is done by only fitting to the reported data in humans, because of the limitation of livestock infection data. Another limitation we faced is on the National Surveillance System. Errors in the final model may be caused by underreported cases from the private health care centres, asymptomatic transmission, poor reporting to the National Surveillance System or the lack of leptospire data in the environment.

In summary, the leptospirosis transmission model predicts the significant environment factor associated with leptospirosis transmission is flooding. A reduction in contact with a contaminated environment can help to improve disease control. This work can be applied to other leptospirosis epidemic areas where flooding data is provided. Further studies should be carried out to access the role of livestock and other relevant data on the transmission of leptospires. Climate change or extreme weather events can also be modelled to predict the severity of future leptospirosis outbreaks[59]. Based on our results, public health policy maker may guide the people who work close to, or in contaminated environments to avoid potential sources of leptospirosis, or by protecting themselves by wearing boots to reduce the leptospirosis outbreak.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Contributions

SC: conceptualized, developed the model, performed the analysis, revising it critically for important content, wrote the first draft and wrote the manuscript. KCM: participated in its design, analysis and involved in drafting the manuscript. AW: participated in its design and involved in drafting the manuscript. CM: participated in its design, revising it critically for important content and wrote the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Impact of rainfall on the transmission of leptospirosis in Si Sa Ket, Thailand

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Abstract. Leptospirosis is a worldwide zoonotic disease, especially in tropical and sub-tropical countries. In Thailand during the rainy season, agricultural and livestock workers are the main occupational risk groups, who are likely to be in contact with the contaminated environment. In this work, we aimed to study the impact of rainfall on the transmission of leptospirosis using a stochastic cellular automata model in Si Sa Ket, Thailand, which has the highest reported cases from 2014 to 2018. Two bi-dimensional square lattices are created to represent human and contaminated environmental lattices. The reported cases are used to fit with the simulation results by varying the transmission probability. The transmission probability that depends on a sinusoidal function and the rainfall index were compared. This study highlighted that seasonal rainfall contributed to the transmission dynamics of leptospirosis. The total epidemic size, which is the sum of overtime cases, was investigated to find the critical transmission probability from endemic to epidemic state. Further study of other factors such as flooding and temperature, should be investigated for a better understanding of how the transmission of leptospirosis impacts the environment.

Introduction

Leptospirosis is an important bacterial zoonosis of worldwide and mostly affects tropical and subtropical countries [1, 2]. The disease is caused by pathogenic spirochete bacteria, genus *Leptospira* [3], which affects humans and animals. The transmission of this disease to humans or animals can occur by exposure to direct contact with infected animals or indirect via contaminated freshwater, soil, or mud [4]. Humans mostly infected by indirect exposure to a contaminated environment [5]. The time between exposure to symptoms and signs appearance (incubation period) of leptospirosis ranges from 7 to 12 days [4]. The acute phase is usually sudden and characterized by fever, headache and myalgia [5]. Later symptoms may include conjunctival injection, abdominal pain, vomiting, prostration, icterus, anuria or oliguria, cardiac arrhythmia or deficiency, meningeal syndrome and a skin rash [5].

In Thailand, the occupation of farmers and agricultural workers is important, estimated around 30% of the population in 2018 [6]. This occupation is the risk group, i.e., the agricultural workers usually walk barefoot in paddy fields lead to exposure with water for a long period, which may cause skin wounds and mucosae to provide routes of entry for leptospires into the body [7]. According to the epidemiology of leptospirosis, reported cases mostly found in rural areas than urban ones because of the environmental factors mentioned [8].

This bacteria can survive for days to months in water or soil [9, 10], which caused outbreaks occurred typically in the rainy season. Thus, the weather condition is one of the major factors influencing the spread of the bacteria [11]. In Salvador Brazil, the incidence of hospitalized leptospirosis patients was positively associated with increased rainfall [12]. The seasonal pattern of leptospirosis cases was observed along with the correlation of rainfall in India [13] and Sri Lanka [14].

Many studies have been proposed on leptospirosis mathematical models. Triampo et al. presented a mathematical model for the leptospirosis using the rate of transmission from an infected rat to a susceptible human varies with the amount of rainfall in Phrae and Nakhon Ratchasima Thailand [15]. They considered a number of leptospirosis cases in Thailand and shown their numerical simulations [16]. Zaman et al. presented an SIR model of human and vector (rat) population using the real data of Thailand for their numerical simulations [17]. Holt et al. used the SIR model to understand the behavior of infection in an African rodent of Tanzania [18]. Pongsumpun et al. developed the SIR-SI model to study the behavior of leptospirosis disease, represented the rate of change for both the vector (rat) and human population [19].

However, those of study did not consider in spatial aspect. The Stochastic Cellular Automata (SCA) is the model that used to describe the spatial dynamics, which are dynamical systems, discrete in space and time [20]. Each lattice of cell can assume a state in a finite set, which can change at every time step based on the transition rules and the state of cell or its neighbor. This model allows to study the environmental transmission for leptospirosis. Previously, Athithan presented a Cellular Automata based computational model for the spread of leptospirosis between human and animal using voting rules [21]. The simulation results are compared with the real data of leptospirosis infection in Thailand during 2000 and 2001. They found that the results were closely in match with the data. However due to the complexity of leptospirosis transmission, the environmental lattice should consider. The probability of changing status of human should depend weather condition and seasonal effect [13].

In this work, we developed the Stochastic Cellular Automata model using heterogeneous rules which consist of two bi-dimensional lattices, i.e., human and environmental lattices for leptospirosis transmission. We aimed to study the impact of transmission rate depends on the rainfall. The model was based on the rural shape of Si Sa Ket Thailand. In the model, we investigated the epidemic size to find the critical transmission probability from endemic to epidemic state.

Method

Data collection

In this study, we study the leptospirosis outbreak of Si Sa Ket Thailand. Data were collected from the national disease surveillance, Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand [22]. Data collection was performed as a part of routine clinical examination procedures.

The amount of daily rainfall for the duration of the study 2014–2018 was obtained from the real-time TRMM Multi-Satellite Precipitation Analysis [23]. We derived daily precipitation from 3B42RT. The daily accumulated precipitation is obtained from TRMM 3B42RT Daily [15, 24].

Model

The proposed SCA model is constructed based on the existing knowledge about leptospirosis transmission. There are two bi-dimensional square lattice size (1000×1000) where a cell is in position (i,j). The total population is assumed to be 350,000 individuals, who have agricultural and farmer worker at Si Sa Ket. Each individual (H_{ij}) is chosen randomly on a cell. Thus, human lattice will consist of occupation or empty site. Human individual can assume to be one of four states, which is in a susceptible state (S), an exposed state (E), an infectious state (I), and a recovered state (R) as illustrated in figure 1. The environment lattice can contain both empty sites and contaminated environment (representing the source of leptospirosis if infected), which estimated to 60% of lattice size as illustrated in figure 1. To simplify the model, we assumed that contaminated environment cell can transmit the infection to humans. In this model, we used the periodic boundary condition and take each time step to correspond to one day.

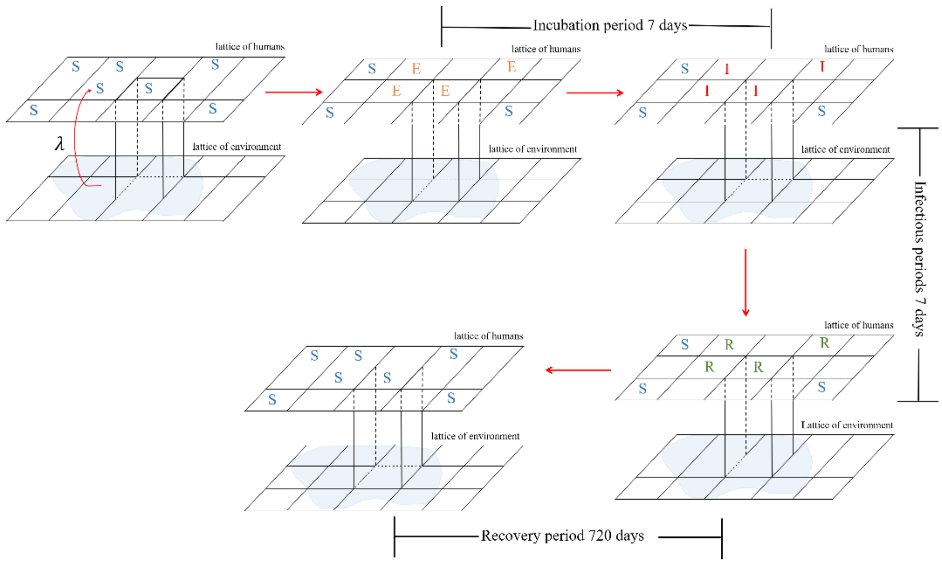

Figure 1. Schematic illustration of the transition state of the Stochastic Cellular Automata model.

In this work, we assumed humans individual, who are not infect with leptospires, randomly chosen move into empty site with probability ρ_{mob} = 0.5 [25] in each day. The length of human movement depends on the probability of the exponential step length, which is $P(r) = (r + \Delta r_0)^{-\beta} e^{-r/\kappa}$ with exponent β=1.75, Δr_0=1.5 km and cutoff values κ=80 km [26]. People can move within the maximum of half length (1000/2). The angle of movement is randomly chosen from a uniform distribution $[0, 2\pi]$. The parameters for the human population and mobility are shown in Table 1.

After human movement, if the position of the susceptible individual matches with the contaminated environment cell, the susceptible individual will gets infect with transmission rate (λ) to be exposed state. An exposed individual becomes an infected individual after a latent period of fixed length τ_E. An infected individual will infect for τ_I period then become a recovered state. This recovered individual will become an again susceptible period of fixed length τ_R.

To study the impact of rainfall, the transmission rate depends on the rainfall index ($R(t)$) as in equation (1) compared to null hypothesis as a sinusoidal function (equation (2)). The transmission rate (λ) is assumed as a linear proportional of environmental variables to test different hypotheses given by:

$$\lambda_1(t) = n_0 + n_1(R(t) - \tau) \quad (1)$$

$$\lambda_2(t) = n_0 + n_1(1 + \sin(2\pi t/365) - \tau) \quad (2)$$

where n_0 and n_1 are constant values. The reported data during 2014 and 2018 is used to fit with the simulation results. The parameters n_0 and n_1 were chosen, where the Mean Square Error (MSE) is minimized.

Table 1. Parameters for human and environmental lattices.

Description	Symbol	Values
Human population size	N_H	350,000
Daily rate of human mobility	ρ_{mob}	0.5 [25]
Water area density in environmental lattice	ρ_E	0.6
Incubation period for human	τ_E	7 days [4]
Duration of infection for human	τ_I	7 days [4]
Duration of loss immunity for human	τ_R	720 days (estimated)

Result /discussion

In this work, we aimed to study the impact of transmission rate depend on the rainfall index compared to sinusoidal function using the SCA model in Si Sa Ket, Thailand. We found the rainfall index more impact than sinusoidal function, which showed better fit with reported cases.

Figure 2 showed the relation between reported cases of leptospirosis, normalized rainfall index, and sinusoidal function. The number of reported cases all year round showed a seasonality pattern. The peak of leptospirosis curve occurred between August and October correspond to the rainy season. We found the peak of reported cases correspond to the peak of rainfall index and sinusoidal curve.

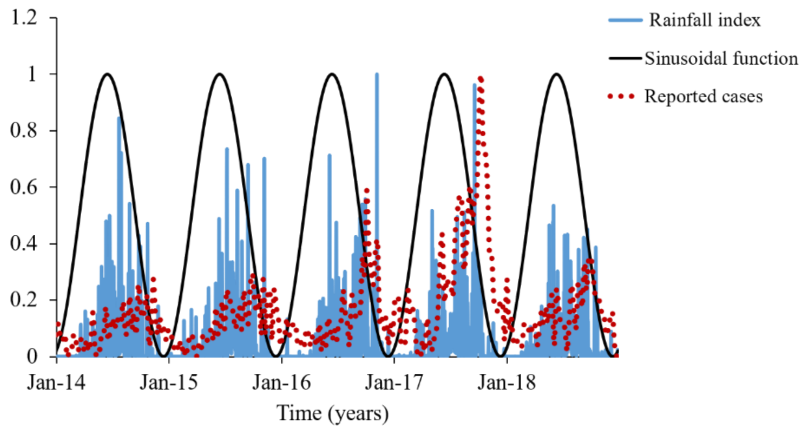

Figure 2. The relation between reported cases of leptospirosis, normalization rainfall index and the sinusoidal function for 2014-2018.

We varied time lag of the sinusoidal function, found that time lag of 4 weeks consistent with reports cases. We compared the real data and simulation results using mean square error (MSE), which found the minimized of MSE equal to 64.30 (figure 3). However, this function captured the reported cases only for the small value. The simulation result of the transmission rate depends on rainfall index with the associations observed at time lag of 2 weeks, which correspond to previous study [27]. The peak of leptospirosis cases corresponds with the peak of simulation results in almost every year. However, it could not describe the data on 2017 due to the other factor such as monsoon and heavy rainfall [28]. In fitting process, our results suggested that using rainfall index fit better than a sinusoidal function, which found MSE equal to 47.35. This finding indicate that the rainfall index contributed to the transmission dynamics of leptospirosis. Although, the sinusoidal function has been commonly used to represent seasonality in epidemic models [29].

The epidemic of leptospirosis are known to be a seasonal pattern. Rainfall is an important risk factor for leptospirosis outbreaks and strongly associated with the tropical settings [30-32]. The heavy rainfall washes superficial soils, bringing pathogenic leptospires in freshwater bodies, where humans will be exposed. Massive leptospirosis outbreaks usually emerge following waterlogging. After heavy rainfall, this pathogen can survive for days to months in a contaminated environment [33].

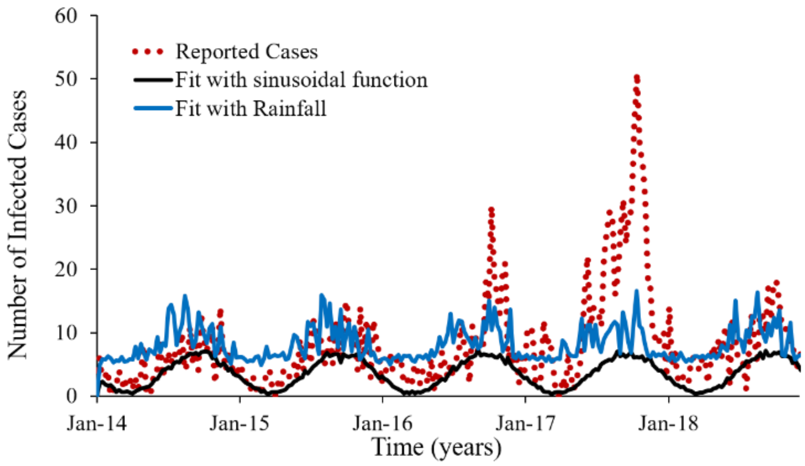

Figure 3. The reported cases of leptospirosis and the simulation result prediction of the transmission depend on the sinusoidal function $n_0 = 3.47 \times 10^{-7}$ $n_1 = 2.09 \times 10^{-6}$ and the rainfall index $n_0 = 4.01 \times 10^{-6}$ and $n_1 = 3.21 \times 10^{-5}$.

In various types of epidemic models, it has been the central issue of how the final epidemic size is determined by the individual system parameters or the composite of them [34]. In this study, we defined the final epidemic size as the fraction of recovered at steady state. To investigate the transmission rate contributes to the final epidemic size in our model, we set the transmission rate be a constant value ($\lambda = n_0$). The critical transmission rate is showed in figure 3, suggests that point transition from endemic phase to epidemic state.

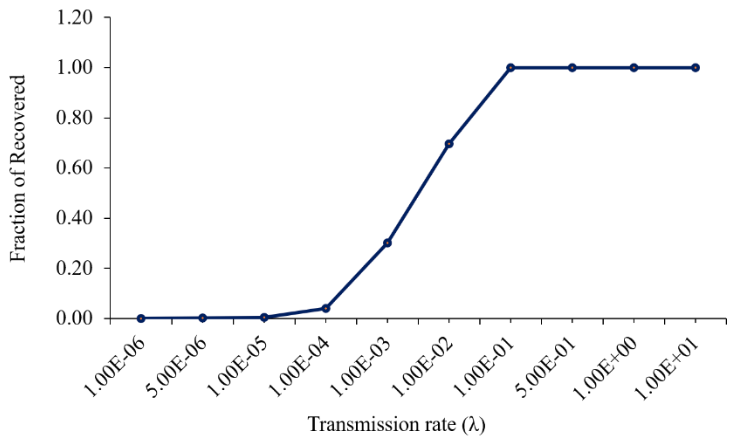

Figure 3. The final epidemic size as predicted by the SEIR model is shown with respect to the transmission rate $\lambda = 1 \times 10^{-6} - 1 \times 10^{1}$.

In conclusion, our results highlighted that the transmission rate depends on rainfall index with time lag 2 weeks capture has impact on the leptospirosis outbreak in Si Sa Ket. We also find the critical transmission rate, which can be basic idea to control the outbreak. However, there are several factors could influence to leptospirosis such as flooding, temperature and humidity. Further study of other factors should be investigated for a better understanding of how the transmission of leptospirosis impacts the environment.

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8. Output (Acknowledge the Thailand Research Fund)

8.1 Chadsuthi, S., Chalvet-Monfray, K., Wiratsudakul, A., Suwancharoen, D. & Cappelle, J. A remotely sensed flooding indicator associated with cattle and buffalo leptospirosis cases in Thailand 2011–2013. *BMC infectious diseases* 18, 602 (2018).

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BMC Infectious Diseases

RESEARCH ARTICLE **Open Access**

A remotely sensed flooding indicator associated with cattle and buffalo leptospirosis cases in Thailand 2011–2013

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Abstract

Background: Leptospirosis is an important zoonotic disease worldwide, caused by spirochetes bacteria of the genus *Leptospira*. In Thailand, cattle and buffalo used in agriculture are in close contact with human beings. During flooding, bacteria can quickly spread throughout an environment, increasing the risk of leptospirosis infection. The aim of this study was to investigate the association of several environmental factors with cattle and buffalo leptospirosis cases in Thailand, with a focus on flooding.

Method: A total of 3571 urine samples were collected from cattle and buffalo in 107 districts by field veterinarians from January 2011 to February 2013. All samples were examined for the presence of leptospirosis infection by loop-mediated isothermal amplification (LAMP). Environmental data, including rainfall, percentage of flooded area (estimated by remote sensing), average elevation, and human and livestock population density were used to build a generalized linear mixed model.

Results: A total of 311 out of 3571 (8.43%) urine samples tested positive by the LAMP technique. Positive samples were recorded in 51 out of 107 districts (47.66%). Results showed a significant association between the percentage of the area flooded at district level and leptospirosis infection in cattle and buffalo ($p = 0.023$). Using this data, a map with a predicted risk of leptospirosis can be developed to help forecast leptospirosis cases in the field.

Conclusions: Our model allows the identification of areas and periods when the risk of leptospirosis infection is higher in cattle and buffalo, mainly due to a seasonal flooding. The increased risk of leptospirosis infection can also be higher in humans too. These areas and periods should be targeted for leptospirosis surveillance and control in both humans and animals.

Keywords: Leptospirosis, Flooding, Buffalo, Cattle, Thailand, Satellite imagery

Background

Leptospirosis is an important worldwide zoonotic disease, caused by spirochetes bacteria of the genus *Leptospira* [1, 2]. This bacteria is classified into pathogenic and nonpathogenic species, with more than 250 pathogenic serovars [1–3]. The disease is particularly important in tropical and subtropical countries. Human and animal infections can occur through direct exposure to infected animals or to indirect exposure to the soil or water contaminated with urine from an infected animal through skin abrasions or mucous membranes [1, 2].

In livestock, it is considered one of the most important diseases, particularly in cattle due to reproductive failures (such as abortion, embryonic death, stillbirths and weak off-spring), decreased milk production and growth rates [1, 4–6]. This results in significant economic losses [7] given the importance of these animals in tropical countries. In Thailand, about 4.4 million beef cattle, 0.51 million dairy cattle, and 0.89 million buffaloes were raised by 770,000, 160,000 and 200,000 households in 2012, respectively [8]. In rural areas, cattle and buffalo live in close contact with agricultural workers, and can

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be a major source of leptospirosis in humans, as highlighted by the predominance of the same serovars in both livestock and humans [4, 9]. Furthermore, a relatively high prevalence of leptospirosis have been detected in the urine of cattle and buffalo in Thailand [10]. An important route of transmission of *Leptospira* from livestock to humans could then be through contaminated urine [1, 2]. And as a consequence, flooding may be an important factor facilitating the transmission of *Leptospira* from livestock to humans and other animals by facilitating the spread of bacteria in wet soils and surface water, where the bacteria can survive for several weeks or months [11].

In humans, the number of reported leptospirosis cases in Thailand is highest after the peak in the rainy season [12]. Higher numbers of leptospirosis cases have been reported following rain or flooding in tropical and subtropical areas (e.g., Laos [13], Guyana [14], and Sri Lanka [15]). In Thailand, most reported cases occurred in northern and northeastern regions, where the main occupation is rice farming. Agricultural workers are the most exposed to biological contaminates in the environment. A previous study in Thailand found that human leptospirosis infections were observed near rivers, and mostly in rice fields likely to have flooding [16]. Furthermore, heavy rain and flooding have been identified as environmental drivers of leptospirosis infections in animals [17]. In the same way, leptospirosis infection risk is associated with flooding in Laos, particularly for human beings who have behaviors and activities involving contact with floodwater [13]. Overall, flooding appears as an important driver of leptospirosis infection in both humans and animals. By taking into account the seasonal variations of flooding using remotely sensed indicators, it may help in anticipating the risk of leptospirosis infection and identify periods and areas for increased surveillance and prevention [18].

The main objective of this study was to investigate the association of several environmental factors (especially remotely sensed indicators of flooding) with cattle and buffalo leptospirosis cases in Thailand. A model of leptospirosis infection risk at the district level was produced, taking into account seasonal flooding.

Materials and methods

Epidemiological data

A total of 3571 urine samples derived from 488 buffalo and 3083 cattle, were collected from January 2011 to February 2013 under a cross-sectional program, which has been described in detail in a recent article [4]. The sampling process was prepared by the provincial Department of Livestock Development livestock officers in 107 districts from 28 provinces, and the samples were randomly selected from each region of Thailand [4]. The sample size was calculated using the multi-stage clustered sampling technique. Three provinces in each of the 9 livestock administrative regions were chosen to represent the area. Subsequently, districts within the provinces were sampled. The target sample size in each region was calculated with the method proposed by Yamane [19]. In this study, we combined 9 regions of Thailand into 4 parts with different climate and seasonal flooding patterns, i.e. the Northern part, subdivided into the Upper Northern and Lower Northern, Central part, which consists of Central, Western and Eastern sub-regions, Northeast part, which consist of Upper Northeastern and Lower Northeastern regions, and the South, which consist of Upper Southern and Lower Southern regions. In their study, the number of samples in each district was not controlled. Sampling was not systematically repeated in all districts, but data was collected during the whole year in the different districts. All urine samples were examined for the presence/absence of leptospiral infection by loop-mediated isothermal amplification (LAMP) method [4, 10]. This technique showed high sensitivity and specificity at 96.8 and 97.0%, respectively [10].

Environmental data

The environmental variables tested in our study include rainfall, flooded area, elevation, and human and livestock population densities. Flooding is an important driver of leptospirosis, but no data is readily available. The flooding variable was calculated based on the modified normalized difference water index (MNDWI). Other variables were collected from national or international databases. All variables were aggregated at the district level to match the spatial resolution of the epidemiological data.

The amount of rainfall was obtained from near Real-time TRMM (Tropical Rainfall Measuring Mission) multi-satellite precipitation analysis (TMPA-RT), which is produced at the National Aeronautics and Space Administration, Goddard Earth Sciences Data and Information Services Center (NASA GES DISC) [20]. The daily accumulated precipitation product is generated from the Near Real-Time Precipitation 3-hourly 1 day TMPA at a spatial resolution of 0.25 degree × 0.25 degree Version 7 (TRMM 3B42RT Daily) [21, 22]. In this study, given the homogeneity of rainfall at the district level, we only extracted the TRMM data at the centroid of each district.

To identify flooded areas, we used the data from the Moderate Resolution Imaging Spectroradiometer (MODIS) of the Terra satellite (Surface Reflectance 8-Day L3 Global 500 m SIN Grid V005 (MOD09A1)). In each image pixel, the data provides an estimation of the surface spectral reflectance measured at ground level in the absence of atmospheric scattering or absorption. The band 4 (green) and band 7 (infrared) were used to calculate the modified normalized difference water index (MNDWI) [18, 23], which allows an estimate of the water presence in each pixel. Within all districts, each pixel was classified as flooded if the MNDWI value was more than or equal to zero. This threshold of zero for MNDWI is in the range of optimal thresholds calibrated in previous studies [23–25]. Permanent water bodies such as rivers and lakes were masked out using QGIS version 2.8.3 [26]. Then, the number of flooded pixels were counted to calculate the percentage of flooded land in each district.

Elevation can be associated with slopes and increased movement of surface water [27], but slope data was not available at a national scale in Thailand. Elevation data was derived from the NASA Shuttle Radar Topographic Mission (SRTM) 90 m Digital Elevation Data, which provides elevation data for the entire world (http://srtm.csi.cgiar.org/index.asp). The average elevation at the district level was used in the model.

Human population data was obtained from the WorldPop database, which presents the number of people per hectare (http://www.worldpop.org.uk) (Additional file 2: Figure S5). Human population density was included in the model because it could be associated with different agricultural practices in areas with different levels of economic development. The animal population density of livestock species (buffalo, cattle, goat, pigs and sheep) were obtained from the Information and Communication Technology Center (ICT), Department of Livestock Development of Thailand at the district level (http://ict.dld.go.th) (Additional file 2: Figure S5). Goats, pigs and sheep were included because they may also contribute to the circulation of leptospirosis in cattle and buffaloes. Seroprevalences of other livestock were shown in Thailand from January to August 2001 in a previous study [28]. In this study, no urine samples were collected in urban districts because limited number of cattle and buffaloes are found in areas of high human population density. The districts with a human population density above 1400 people/km^2, which corresponds to the urban centers of the main cities of Thailand, and no livestock were not included in the risk mapping given the limited number of animals in urban centers.

Statistical analysis

To investigate the association between the risk factors listed in the previous paragraph (explanatory variables with a fixed effect) and leptospirosis infection (the response variable), we first study univariate linear regressions. Using a generalized linear mixed model (GLMM) with a logit link since the response variable had a binomial distribution. We used R software [29] with the package lme4 [30]. Since all individual urine samples were not independent because they were collected during common sampling occasions, we used the sampling occasion index as a random effect variable. Each sampling occasion was identified by a date, a year and a district geocode. The best multivariable model was selected using a stepwise backward approach based on the Akaike Information Criterion (AIC). The Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC) plot was used to estimate the model performance. We also used cross-validation to measure the performance of the best model. Data was randomly split into training (2/3 of data) and test (1/3 of data) sets. Training data is used to produce the prediction model, while the test data is used to test the model performance. Given the size of our dataset, we chose to keep 2/3 of the data in the training set to optimize model performance. We performed repeated cross-validations 1000 times to estimate the mean and standard deviation of the cross-validated AUC (cvAUC) of the best model.

The best model was used to predict leptospirosis infection risk in 2012 and 2016 for three periods (mid-January, mid-May and mid-September) which represents the middle of the dry season, the beginning of the rainy season and the end of the rainy season, respectively for central and northern Thailand.

Results

A total of 3571 urine samples of cattle and buffalo were tested by the LAMP technique. 311 samples were positive. The overall uroprevalence over 107 districts is presented in Fig. 1. Positive samples were recorded in 51 districts (47.66% of districts). From the temporal aspect, higher prevalence was observed in May (Fig. 2), which is the beginning of the rainy season in the central and northern part of Thailand [31].

The results of the univariate linear regressions show that the percentage of flooded area and the percentage of flooded area with a 1 month lag were found to be significant (Additional file 1:Table S1). The risk of livestock infection was higher if the percentage of flood area was higher.

Three explanatory variables were kept in the final model based on the stepwise backward approach: the percentage of flooded area, human and livestock population densities (Table 1). This final model was applied to predict the risk of *Leptospira* presence at the district level, it showed high performance with an AUC of 0.8861 (Fig. 3). The percentage of flooded area was the only variable significantly associated with the prevalence of leptospirosis in cattle and buffalo in the GLMM ($p = 0.023$, Table 1). The cvAUC had a mean of 0.6427 (sd = 0.0827). The distribution of the 1000 estimations of the cvAUC is shown in Fig. 4.

Maps of leptospirosis infection risk were produced from the final model in the middle of January, May, and

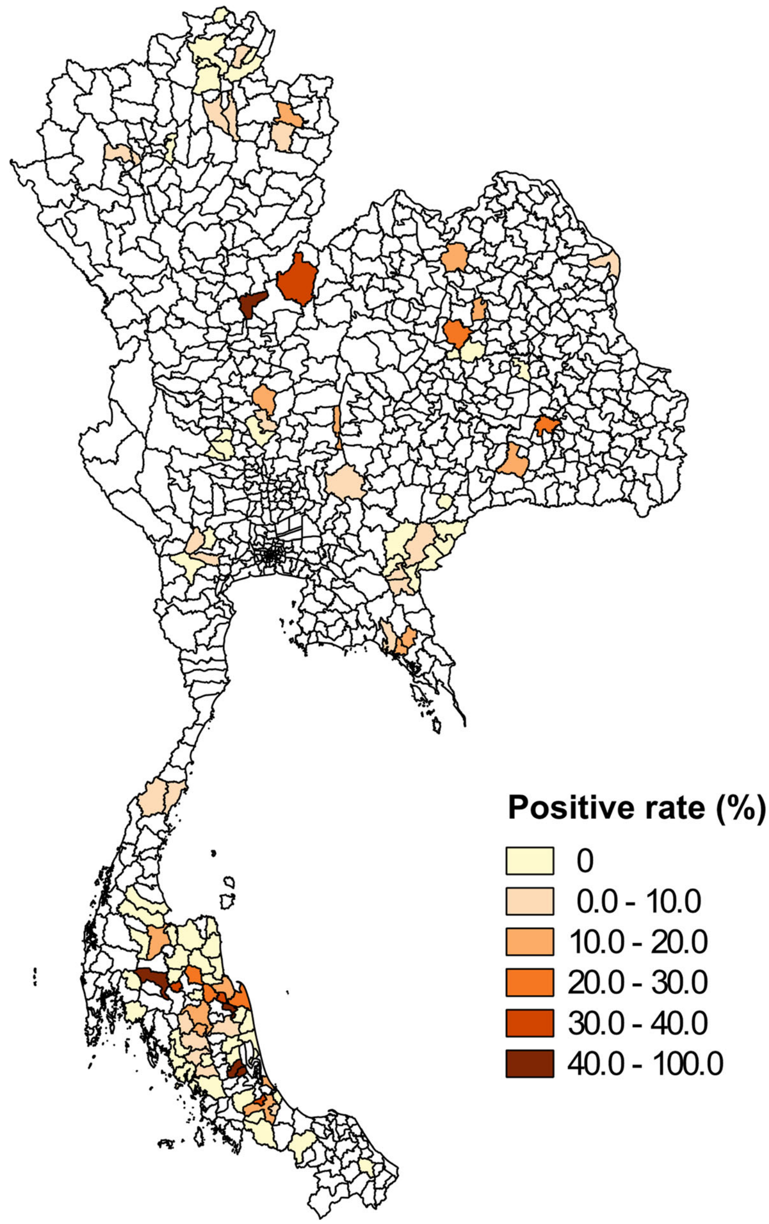

Fig. 1 Map of the positive rate of leptospirosis in cattle and buffalo in 107 districts of Thailand. Urine samples were tested by LAMP. The non-sampled districts are presented in white

September in 2012, which corresponds to the period when most data were collected (Fig. 5). As expected from the results of the model, the areas of increased leptospirosis risk vary seasonally (Fig. 5) and are found in the regions with a high percentage of area flooded (Additional file 2: Figure S1). The districts with a high leptospirosis infection risk in mid-January were mostly located in the southern part of Thailand, especially in the south-east coastal regions, i.e. during the high rainfall period in this area (Additional file 2: Figure S2) [31]. In mid-May, high leptospirosis infection risk mostly occurs in northern and north-eastern parts, which correspond to the beginning of the rainy season in this part of Thailand. In mid-September, high leptospirosis infection risk areas occurred in all parts except for the southern part, and was particularly high in the central part. In this analysis, the final model was also used to predict the leptospirosis infection risk in 2016 (Additional file 2: Figure S3). The leptospirosis infection risk districts were also mostly found in regions with a high percentage of flooded area (Additional file 2: Figure S4).

Discussion

This study investigates the relation between cattle and buffalo leptospirosis infections and flooding based on

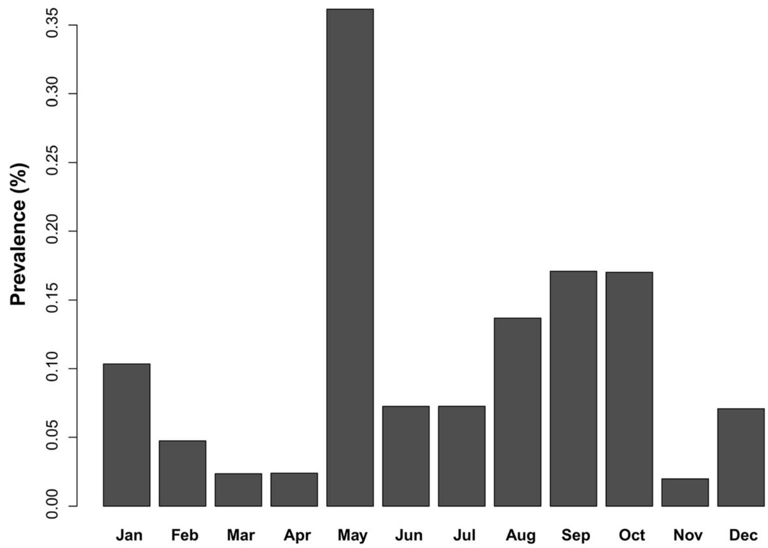

Fig. 2 The leptospirosis prevalence observed per month in both cattle and buffalo for 2011–2013

cross-sectional surveillance during 2011–2013 in Thailand. This analysis provides, to our knowledge, the first predictive risk mapping for cattle and buffalo leptospirosis in Thailand. The temporal and spatial variations of leptospirosis infection in Thailand appears to be associated with flooding.

Results of the GLMM show a significant association between the percentage of flood area and leptospirosis infection in cattle and buffalo at the district level. The flooding area was evaluated using a remote sensing indicator [18, 23]. This finding suggests that exposure to flooding increases the risk of leptospirosis infection for cattle and buffalo. Most of the samples used in this study were collected in rural areas. In these areas, the soil may become contaminated with leptospires because of the presence of infected animals. When flooding or heavy rainfall occurs, the water picks up contaminated soil and animal excreta from the soil. This results in the spread of leptospirosis through contaminated water [32, 33]. Flooding could possibly be the principal reason for leptospirosis epidemics above other factors [34]. This is consistent with other studies showing that local flooding can play an important role in leptospirosis transmission [17, 18, 34]. Therefore, flood control could be an option to reduce the risk of leptospirosis infection in animals, which can be a major reservoir for human infection [4, 9].

Furthermore, the results of the univariate linear regressions show that the flooding factor is the only significant factor and is a better indicator than the amount of rainfall and the accumulation of rainfall. It may be because rainfall does not directly influence leptospirosis transmission while flooding facilitating it. Rainfall has previously been associated with leptospirosis but often with a time lag of 1–3 months [35, 36] which is likely the lag between rainfall and flooding. A remotely sensed flooding indicator is likely to be a more accurate predictor of the risk of leptospirosis infection than using rainfall.

The predicted risk maps of leptospirosis infection were created based on the final model for 3 periods in 2012. In each part of Thailand, higher infection risk was observed during the first floods after a dry period in that part of the country. This influence of the first flood of the year has been suggested in other studies [18]. It could be responsible for the rapid dissemination of leptospires concentrated in small areas during the dry season. High prevalence in livestock is not predicted in the same period for the whole Thailand. Three main periods

Table 1 Results of the best generalized linear mixed model as selected by a stepwise backward approach with the AIC

Variable	Odd Ratio	95% Confidence Interval	*p*-value
Intercept	0.0309	0.0183–0.0473	<2e-16***
Percentage of flood area	1.5794	1.0611–2.3629	0.023*
Human population density	1.3495	0.9511–1.9016	0.084
Livestock population density	0.5989	0.3079–1.0957	0.105

*$p < 0.05$, ***$p < 0.001$

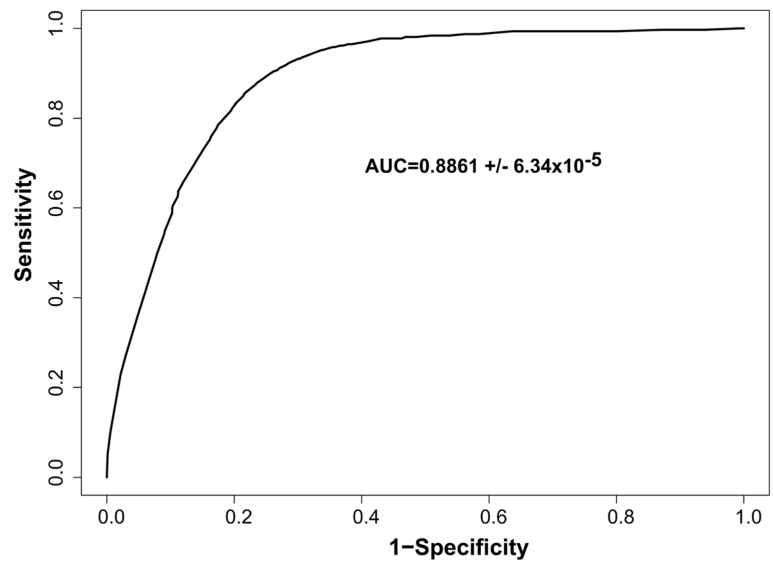

Fig. 3 ROC curve of the best generalized linear mixed model

of risk can be identified and associated with three different parts of Thailand (i.e., Northern, Central and Southern parts) and are related with the periods of flooding. The difference in these flooding periods is mainly due to two factors: a) the difference of rainfall seasonality between southern Thailand and the rest of the country, and b) the delay between rainfall and flooding between the central part and the northeastern part of the country. The central part of the country is downstream of the most important rivers in Thailand, and major flooding occurs later than in the rest of the country, in September to November, with an increased intensity. This explains why high risk occurs for most districts in this period, which also corresponds to its high population [12].

With the backward step approach, the final model includes human and livestock population densities. However, the model results show that those variables are not significant. Furthermore, these variables should be interpreted very cautiously because several confounding factors could be involved. Thus, they were kept because they improved the final model (based on the decrease of the AIC), but they should not be over-interpreted.

Our study was based on a cross-sectional survey [4], which was limited as there may be procedural concerns.

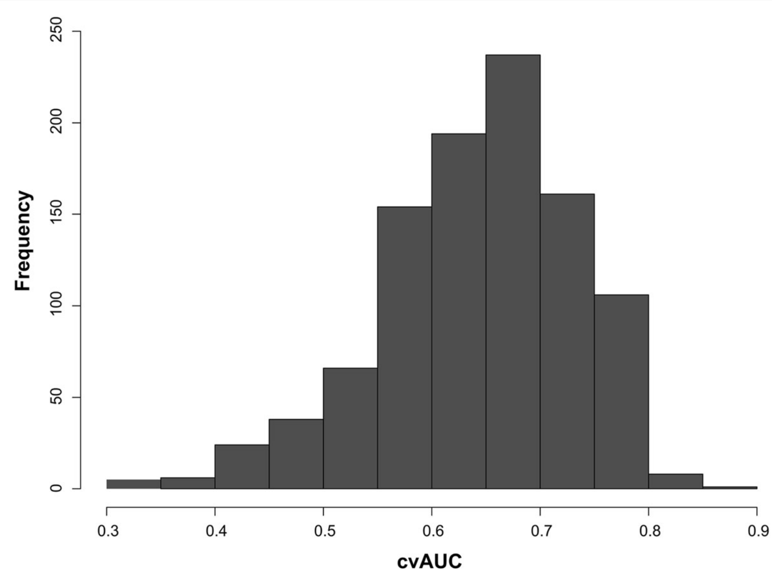

Fig. 4 The cross-validated AUC distribution

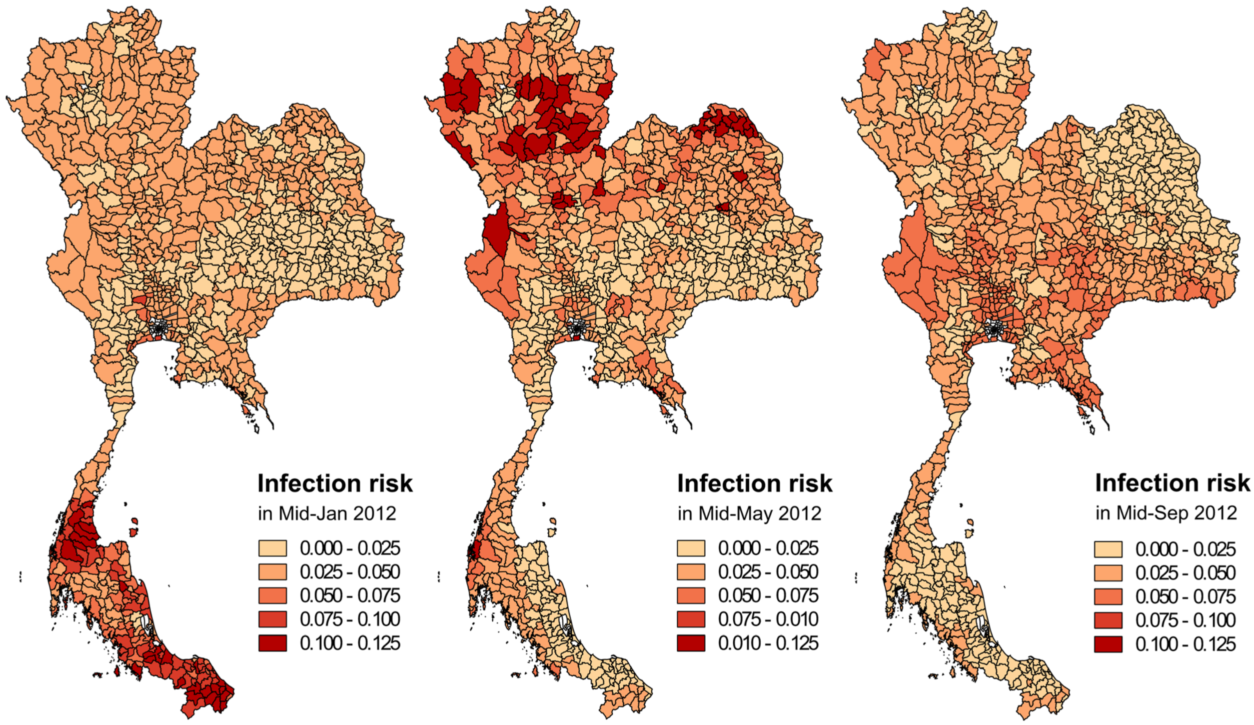

Fig. 5 Map of the prediction of leptospirosis infection risk using the final multivariate linear regression model in three different periods of 2012. A leptospirosis infection risk of 0.1 indicates that approximately 1/10 livestock are expected to be positive by LAMP for leptospirosis infection. The non-predicted districts are presented in white

It does not provide data for all districts in the country and for all seasons in each district. A longitudinal survey is strongly suggested in further studies, with repeated sampling in a larger number of districts in the whole country. It would provide better data to understand the seasonality of leptospirosis infection and could provide a more accurate disease transmission model. The samples in each district were mostly collected only once. However, the samples were distributed over every part of Thailand for all seasons. Furthermore, the model had a relatively good performance (AUC =0.8861) but a lower and quite variable cross-validated AUC (mean cvAUC = 0.6427, sd = 0.0827, Fig. 4). This difference between AUC and cvAUC, and the variability of the cvAUC may be explained by the relatively small size of our dataset at the district level leading to a small validation dataset (71 districts for the training dataset and only 36 for the validation dataset). Furthermore, given this size limit, some validation datasets may include a different proportion of southern districts than their matching training datasets. The difference of flooding patterns between southern Thailand and the rest of the country may then further explain the lower cvAUC. Training the model on a larger dataset and having an independent large dataset to validate it would help build a more robust model.

The presence of pathogenic leptospires in livestock was tested with LAMP [4, 10], which allows a simple and rapid diagnosis of leptospirosis with high accuracy. However, this technique cannot provide any genotypic information, thus could not be used to compare pathogenic strains in the study. However, in Thailand, the accuracy of LAMP (97.0%) was higher than real-time PCR (91.9%) [10]. Thus, results from this technique can be used with confidence in our study to investigate the association of livestock leptospirosis infection with environmental factors.

Other environmental risk factors such as soil type and land use, which were not explored in this study, may be required to better characterize leptospirosis infection risk. A previous study showed that agricultural land and clay loams soil are significantly associated with leptospirosis infection in humans [37]. These factors could influence the identification of high-risk areas and help improve our model.

Other individual variables such as sex and age of the animals investigated were not considered in this study due to data limits. These factors could help us to improve the model and may impact the results [38, 39]. *Leptospira* can infect a wide range of livestock including pigs, goats and sheep [40, 41]. Studies of these animals should also be implemented as they may also contribute to leptospirosis epidemics. However, the present study focused on the flooding indicator associated with cattle and buffalo infection. The good performance of the model shows that flooding is a major factor that should be considered in leptospirosis risk models.

Conclusion

Our findings could identify flooding as a major driver of the risk of leptospirosis infection in cattle and buffalo. Public awareness about the risk of leptospirosis during flooding should be raised in order for people to take prevention measures when possible. The risk maps could also help to develop effective intervention strategies and optimize the allocation of public health resources, veterinary care and control measures. A high level of livestock infection could increase the risk to human health due to contact with infected animals or a contaminated environment by the urine of infected animals [2, 34]. Livestock may then play an important role as a potential indicator of high-risk areas for leptospirosis in humans. Further study needs to be done to assess the risks associated with contact between livestock and humans. In this regard, further data needs to be collected and made available.

Additional files

Additional file 1: Table S1. Summary results of the univariable linear regression model (with binomial function and random effect). (DOCX 14 kb)

Additional file 2: Figure S1. Percentage of flood area in 2012. **Figure S2.** The monthly rainfall of Thailand in 2012. **Figure S3.** Prediction of leptospirosis infection risk in 2016. The non-predicted districts are presented in white. **Figure S4.** Percentage of Flood area in 2016. **Figure S5.** Maps of human density (people/km^2) and livestock density (animal/km^2). (DOCX 3416 kb)

Abbreviations

AIC: Akaike Information Criterion; AUC: Area Under the Curve; GLMM: Generalized linear mixed model; LAMP: Loop-mediated isothermal amplification; MNDWI: Modified normalized difference water index; MODIS: Moderate Resolution Imaging Spectroradiometer; ROC: Receiver Operating Characteristic; SRTM: Shuttle Radar Topographic Mission; TRMM: Tropical Rainfall Measuring Mission

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Availability of data and materials

The data supporting the findings can be found in the main paper and in additional supporting files.

Authors' contributions

SC: conceptualized, participated in its design, performed the analysis, revising it critically for important content, wrote the first draft and wrote the manuscript. JC: conceptualized, participated in its design, analysis, revising it critically for important content, and wrote the manuscript. KCM: participated in its design, analysis and involved in drafting the manuscript. AW: involved in drafting the manuscript, participated in acquisition of data and revising it critically for important content. DS SC JC: participated in data extraction and interpretation. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The need for approval was waived as this study used published animal data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Modelling Leptospirosis transmission in Thailand: accessing the impact of flooding and weather conditions

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Abstract

The epidemic of leptospirosis in humans continues to this day, causing incidences annually in Thailand. We developed a mathematical model to study the transmission dynamics between humans, animals, and a contaminated environment. We compared different models that included the impact of flooding and weather conditions on the transmission rate from a contaminated environment, the leptospire shedding rate and the multiplication rate of the leptospires in the environment. We found that the model with the transmission rate dependent on flooding and temperature best-fit the reported human data on leptospirosis in Thailand. Our results highlight that flooding indicators have the most impact on transmission, indicating a high degree of flooding leads to higher cases. Sensitivity analysis showed that the transmission of leptospires from the contaminated environment was the most important parameter for the total number of human cases. Our results suggest that public health policy makers should guide the people who work close to, or in contaminated environments to avoiding potential sources of leptospirosis, or by protecting themselves by wearing boots to reduce the leptospirosis outbreak.

Keywords: Leptospirosis, transmission dynamics, Flooding, Weather conditions

Introduction

Leptospirosis is a worldwide zoonotic bacterial disease, that is particularly endemic in tropical and subtropical countries[1,2]. The infection of humans is mainly caused by direct contact with an infected animals and also by indirect contact with urine of infected animals through cuts in the skin or mucous membranes in a contaminated environment[1,3].

In humans, the epidemic of leptospirosis continues to this day, causing incidences annually. The highest number of cases reported in Thailand is during the rainy season in mid-May to mid-October[4]. High-risk groups include farmers and other agricultural workers, who are likely to come into contact with infected animals, and contaminated wet soil and water during their daily activities[5-7]. In addition, leptospirosis in livestock is also considered an important disease, causing reproductive failures (such as abortion, embryonic death, stillbirths, and weak off-spring), decreased milk production and growth rates[8-11]. A relatively high prevalence of leptospirosis has been detected in the urine of cattle and buffalo in Thailand[8]. Contact with infected livestock during production was also investigated, and was found to increase the risk of infection[12]. This spirochete bacteria are mainly transmitted through injured or cut skin in contact with contaminated water or soil. Leptospires may survive from a few weeks to almost a year in surface water or wet soil even during dry days[13].

Most of the previous leptospirosis models focused on spreading of the disease in humans and rodents[14-16]. However, compartment models of leptospirosis, with links between the host or livestock and the environment, have also been proposed. Babylon *et al*. presented a simple Susceptible-Infective (SI) model to describe the spreading of leptospirosis in lambs in contact with free-living leptsopires[17]. A model to study the leptospire infection dynamics in Norway rat (*Rattus norvegicus*) as the reservoir host in the environment was also presented[18]. However, the model should be composed of human, animals and environmental compartments for leptospirosis infection dynamics. Baca-Carrasco *et al*. presented an SI model to study the transmission in humans and animals and included bacteria in the environment[19]. The direct transmission between animals and humans has also been explored[20].

Thus far, those mathematical models did not consider seasonal effects, flooding or weather conditions. Seasonal and weather conditions have been shown to be associated with an increased leptospirosis risk[12,21-24]. In this work, we propose different leptospirosis transmission models, which considers the impact of environmental factors such as seasonal flooding, and weather conditions. The livestock species, *i.e.*, buffalo, cattle, goats, pigs, and sheep, are the animal reservoirs and contribute to the circulation of leptospirosis in humans and the environment[25,26]. The reported data on human leptospirosis in Thailand was used to fit the transmission models to help identify the factors that influence the leptospirosis transmission dynamics. The proposed transmission models may help to understand the processes of leptospirosis transmission in Thailand and allow more accurate predictions of future outbreaks and better control of the disease.

Methods

Data

In this study, reported cases of human leptospirosis were retrieved from the national disease surveillance (report 506), Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand[27]. Most positive cases were suspected leptospirosis cases, based on the clinical diagnosis made by attending physicians. The clinical criteria for leptospirosis were high fever, chills, headache, with at least one of the following symptoms including abdominal pain, red eyes, neurological symptoms (such as stiffness, abnormal feelings, etc.), and dry cough or cough with bloody sputum, and a career history of exposure to water areas or environments contaminated with animal excreta[28]. Some of the suspected cases were then examined using laboratory tests such as Latex agglutination test (LA), Dipstick test, Lateral flow test, Microcapsule agglutination test (MCAT), Immunofluorescent antibody test (IFA), Microscopic agglutination test (MAT) or ELISA for confirmation. The suspected cases were mainly reported from public hospitals with a small fraction from private hospitals. In this research, we analyzed all reported cases from 2010 to 2016 in two provinces (*i.e.*, Si Sa Ket and Surin), in which the highest number of cases were reported.

Data collection was performed as a part of routine clinical examination procedures of the Thai Ministry of Public Health surveillance and response. Data collection was approved by the Ethics Committee of the Ministry of Public Health of Thailand. Data containing the patient's medical records, without any patient information except location, were de-identified prior to analysis.

The remotely sensed environmental data obtained included the modified normalized difference water index (MNDWI) and the Land Surface Temperature (LST). MNDWI was extracted from the data of the Moderate Resolution Imaging Spectroradiometer (MODIS) of the Terra satellite (Surface Reflectance 8-Day L3 Global 500m SIN Grid V005 (MOD09A1)). We used band 4 (green) and band 7 (infrared) to calculate the Modified Normalized Difference Water Index (MNDWI)[29,30]. Within all provinces, each pixel was classified as flood area if the MNDWI value was greater than or equal to zero[21,30]. Permanent water bodies were masked out using QGIS version 2.8.3[31]. The number of flooded pixels was counted to calculate the index of land flooding, which was then used to calculate the percentage of area flooded.

The LST was extracted from the MODIS Terra product (MOD11A2) with Emissivity 8-Day L3 Global 1 km, which is composed of the daily LST product (MOD11A1) with a 1 km resolution and stored on a 1 km Sinusoidal grid as the average values of clear-sky LSTs during an 8-day period[32].

The amount of rainfall was obtained from the real-time Tropical Rainfall Measuring Mission (TRMM) Multi-Satellite Precipitation Analysis (TMPA-RT)[33]. We derived daily precipitation and daily accumulated precipitation from the TMPA product: 3B42RT[34,35].

The initial human population data were obtained from the WorldPop database, which presents the number of people per pixel (http://www.worldpop.org.uk). The initial livestock population of each specie (buffalo, cattle, goat, pigs, and sheep) was obtained from the Information and Communication Technology Center (ICT), Department of Livestock Development of Thailand at the province level (http://ict.dld.go.th).

Model for leptospirosis transmission

A simple SIR model of two groups is used to study the transmission dynamics of leptospirosis between humans, livestock and the contaminated environment. Susceptible human and livestock individuals are introduced, denoted by S_h and S_a, respectively. S_h and S_a can become infected through contact with infected livestock and/or the contaminated environment. The infected livestock can shed leptospires into the environment and increase the number of leptospires (L compartment) in that province. The hygienic level of the contaminated environment can be defined as the density of leptospires. The leptospires die at a rate μ_L. Infected humans and animals recover at the constant rates γ_h and γ_a, and loss immunity at the rates ν_h and ν_a, respectively. Both population sizes are assumed to be constant. In this work, we developed the transmission model based on previous studies[19,20]. The leptospirosis transmission model is described by the following set of differential equations:

$$
\begin{aligned}
\frac{dS_h(t)}{dt} &= \mu_h N_h - \beta_{ha}(t)\frac{S_h(t)I_a(t)}{N_h} - \beta_{hL}(t)h(t)\frac{S_h(t)}{N_h} + \nu_h R_h(t) - \mu_h S_h(t),\\
\frac{dI_h(t)}{dt} &= \beta_{ha}(t)\frac{S_h(t)I_a(t)}{N_h} + \beta_{hL}(t)h(t)\frac{S_h(t)}{N_h} - \gamma_h I_h(t) - \mu_h I_h(t),\\
\frac{dR_h(t)}{dt} &= \gamma_h I_h(t) - \nu_h R_h(t) - \mu_h R_h(t),\\
\frac{dS_a(t)}{dt} &= \mu_a N_a - \beta_{aa}(t)\frac{S_a(t)I_a(t)}{N_a(t)} - \beta_{aL}(t)h(t)\frac{S_a(t)}{N_a(t)} + \nu_a R_a(t) - \mu_a S_a(t), \qquad (1)\\
\frac{dI_a(t)}{dt} &= \beta_{aa}(t)\frac{S_a(t)I_a(t)}{N_a(t)} + \beta_{aL}(t)h(t)\frac{S_a(t)}{N_a(t)} - \gamma_a I_a(t) - \mu_a I_a(t),\\
\frac{dR_a(t)}{dt} &= \gamma_a I_a(t) - \nu_a R_a(t) - \mu_a R_a(t),\\
\frac{dL(t)}{dt} &= \omega(t)I_a(t) + m(t)g(t)L(t) - \mu_L L(t),
\end{aligned}
$$

where $N = S + I + R$ for livestock and human compartments.

In our model, we assumed that, as a zoonosis disease, the human-human transmission does not exist[10]; thus infection in humans always developed from animal sources or the contaminated environment. The leptospires shedding from humans into the environment is neglected in our study as the likelihood is very low. The function $g(t) = \frac{\chi - L(t)}{\chi}$ in equation (1) represents the logistic growth multiplier, which allows the growth to depend on the current number of leptospires and limits excessive growth, where χ is the maximum carrying capacity, or saturating population size. A saturation term, $h(t) = \frac{L(t)}{L(t)+\kappa}$, is added to limit the effect of transmission due to the large number of leptospires[14,36], where κ is the density of leptospires in the environment at which the transmission rate is $0.5\beta_L(t)$. The diagram of the model and its relationship between the compartments is provided in Fig. 1. A set of parameters is shown in Table 1.

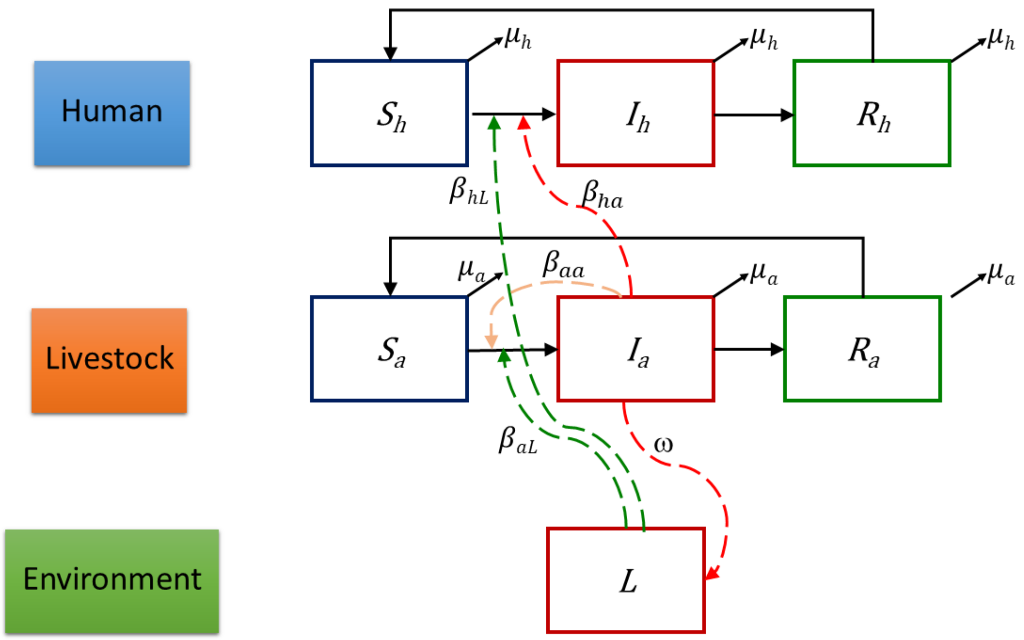

Figure 1. Dynamics of leptospirosis spread between humans, livestock and the contaminated environment. Dashed green arrow shows the transmission route from the contaminated environment to susceptible livestock (S_a) and humans (S_h). Infected livestock (I_h) transmit leptospires to humans and shed to environment (red dashed line) and to livestock (orange dashed line).

Table 1: A set of parameters.

Description	**Symbol**	**Values**
Birth and death rate of humans	$1/\mu^h$	70 years (estimated)
Duration of infection for humans	$1/\gamma^h$	14 days (estimated from[3])
Duration of loss of immunity for humans	$1/\nu^h$	720 days (estimated from[3])
Transmission rate from infected livestock to human	β_{ha}	fitted
Birth and death rate of livestock	$1/\mu^a$	3 years (estimated)
Duration of infection for livestock	$1/\gamma^a$	200 days (estimated from[37])
Duration of loss of immunity for livestock	$1/\nu^a$	540 days (estimated)
Transmission rate from infected livestock to livestock	β_{aa}	fitted

Duration of contamination for the environment	μ_L	0.02381 day^{-1} (estimated from[36])
Density of leptospires at which the transmission rate from the environment is $0.5\beta_L(t)$	κ	10^2 km^{-2} (estimated from[36])
Maximum carrying capacity	χ	$1x10^5$ (estimated)
Density of the free living leptospires in a province at $t = 0$	$L_i(0)$	10^{-3} km^{-2} (estimated from[36])
Density of leptospires shed per infected livestock	ω	fitted
Transmission rate from the contaminated environment to human and livestock	β_{hL} and β_{aL}	fitted
Multiplication rate of the leptospires in the environment	m	fitted

Some of the parameters in equation (1) may be affected by flooding and weather conditions. In this work, we look at how these conditions can affect the transmission from the contaminated environment, leptospire shedding rate, and the multiplication rate.

The most important parameters are the transmission modes from the contaminated environment to susceptible humans and susceptible livestock (β_{hL} and β_{aL}). We hypothesized that the environment could influence the transmission of leptospirosis. Thus, the transmission terms are constructed as a linear function of normalized data of the percentage of flooded area ($f(t)$), total monthly rainfall ($\rho(t)$), and average monthly temperature ($T(t)$). The virulence of leptospires depends on temperature[38], leading to the inclusion of the average temperature, which may impact the transmission model. We examined four forms of transmission rate dependency corresponding to three environmental variables to test different hypotheses. These four transmission rates assumed the rates were linearly proportional to the environmental variable and are as follows:

(1) Flooding (M1-F): The transmission rates are given by:

$$\beta_{hL}(t) = h_1\big(1 + h_2 f(t - \tau_1)\big)$$

$$\beta_{aL}(t) = a_2\big(1 + a_2 f(t - \tau_1)\big)$$

(2) Rainfall (M1-R): The transmission rates are given by:

$$\beta_{hL}(t) = h_1\big(1 + h_2\rho(t - \tau_1)\big)$$

$$\beta_{aL}(t) = a_1\big(1 + a_2\rho(t - \tau_1)\big)$$

(3) Flooding and temperature (M1-FT): The transmission rates are given by:

$$\beta_{hL}(t) = h_1(1 + h_2 f(t - \tau_1) + h_3 T(t - \tau_2))$$

$$\beta_{aL}(t) = a_1(1 + a_2 f(t - \tau_1) + a_3 T(t - \tau_2))$$

(4) Rainfall and temperature (M1-RT): The transmission rates are given by:

$$\beta_{hL}(t) = h_1(1 + h_2\rho(t - \tau_1) + h_3 T(t - \tau_2))$$

$$\beta_{aL}(t) = a_1(1 + a_2\rho(t - \tau_1) + a_3 T(t - \tau_2))$$

where h_i and a_i are constant values (that were fitted) of each function for each transmission rate, and τ_1 and τ_2 are time lags, varying from 0-8 weeks, which are associated with the infection of humans.

The second model (M2-F and M2-R) are the leptospire shedding rate (ω), which is affected by rainfall. Infected livestock shed leptospires into the environment, which will then be a source of exposure for susceptible humans and livestock. The shedding rate can be described as a logistic curve, to limit its effect at high concentrations.

$$\omega(t) = \omega_0\left(\frac{\rho(t-\tau_1)}{\delta+\rho(t-\tau_1)}\right) \text{ and } \omega(t) = \omega_0\left(\frac{f(t-\tau_1)}{\delta+f(t-\tau_1)}\right)$$

where δ is an inferred threshold parameter corresponding to the rate of half of the maximum shedding rate due to rainfall or the effect of flooding.

The last model affects the multiplication rate of the leptospires in the environment (m), which depends on three environmental variables, namely, the percentage of flooding area ($f(t)$), total monthly rainfall ($\rho(t)$) and average monthly temperature ($T(t)$). The multiplication rate is given by:

(1) Flooding (M3-F): $m(t) = x_1(1 + x_2 f(t - \tau_1))$

(2) Rainfall (M3-R): $m(t) = x_1(1 + x_2\rho(t - \tau_1))$

(3) Flooding and temperature (M3-FT): $m(t) = x_1(1 + x_2 f(t - \tau_1) + x_3 T(t - \tau_2))$

(4) Rainfall and temperature (M3-RT): $m(t) = x_1(1 + x_2\rho(t - \tau_1) + x_3 T(t - \tau_2))$

where x_1, x_2 and x_3 are constant values (fitted parameters).

Ten models (M1-F, M1-R, M1-FT, M1-RT, M2-F, M2-R, M3-F, M3-R, M3-FT and M3-RT) were considered individually and compared to the null hypothesis, where all parameters are constant values. The effect of flooding was compared to the effect of rainfall without and with a temperature effect. The combined models that use multiple effects above were also considered. A stochastic simulation approach was employed using a tau-leaping algorithm with a fixed time step[39]. Using the parameters of the best model, 1,000 simulations were generated.

Parameter estimation and sensitivity analysis

To estimate the parameters of our model, we assumed that the epidemic was initiated by free-living leptospires in that area by setting the initial number of free-living leptospires to a low concentration (Table 1). We linked the biweekly human cases from the simulation results with the corresponding actual reported human cases from 2010 to 2015. The best fit was obtained by maximizing a normal log-likelihood estimation, which produced simulation results that were most similar to the reported data. We used the nlminb function in R, which is a quasi-Newton method with a constrained bound, to find the optimal set of parameters[40]. The model that shows the minimum negative log-likelihood was selected as the best model.

In this work, according to previous findings, we considered the effect of time lag (τ) on the environmental data to leptospirosis cases due to transmission. Rainfall has been observed to be associated with leptospirosis, often with a time lag of 1-3 months[41,42]. We set the maximum time lags of flooding and rainfall to be eight weeks. We set the lag period to be the same for the effects of temperature, raining, and flooding in this model[24].

To perform a sensitivity analysis of which parameters influence the effect of leptospirosis transmission the most, we used the Partial Rank Correlation Coefficients (PRCC) technique[43,44]. Then, we used the Latin hypercube sampling(LHS), which is a statistical Monte Carlo sampling technique, to sample the parameters using the lhs package in R[45]. 1,000 parameter sets were sampled with each parameter sampled from a uniform distribution. The PRCC was ranked as a response function to the cumulative new cases in each province using the sensitivity package in R with bootstrapping 1,000 times to obtain a 95% confidence intervals[46]. Based on the linear assumption, positive (negative) PRCC values imply positive (negative) correlations to the response function.

Estimation of time-dependent reproduction number (R_{td})

The basic reproductive number (R_0) is generally defined as the average number of secondary infected individuals caused by an infected individual in a population that is completely susceptible. Due to the complexity of the model and the time-dependent variables, there is no exact way to explain R_0 for this model, as it is a complex function of many different variables. An alternative method, proposed by Wallinga *et al*[47], computes the reproduction number from the observed cases using a likelihood-based method, calculated by averaging the overall transmission networks which makes it fit an epidemic curve[48]. In this work, we calculated a time-dependent reproduction number (R_{td}) according to the R0 package in R[48]. The number of biweekly cases obtained from the simulations of the best model in three provinces was used to estimate R_{td}. The serial interval between successive infections of the reported epidemic was identified and used to estimate the generation time distribution, with the mean and standard deviation (sd) of each province, using the R0 package. Then the R_{td} of each province was estimated with the 95% confidence interval.

Results

Based on the annual reports of leptospirosis cases in Thailand from 2010 to 2016, it appears that the disease continues to spread throughout the country (Fig. 2(A)). The highest number of annual cases was observed mostly in the northeastern region, which also had the highest number of cumulative cases (Fig. 2(B)). In this work, we considered two provinces, namely, Si Sa Ket (highest number of cumulative cases) and Surin (second highest number of cumulative cases) for testing the models. The time series of reported biweekly cases were plotted with the percentage of flooding, the amount of rainfall, and temperature (Fig. S1.). We found that the time series of biweekly reported cases in the two provinces showed a similar trend. The percentage of flooding and the amount of rainfall were found to increase around the same time of year when the number of reported cases increased. However, the temperature was negatively correlated with incident cases.

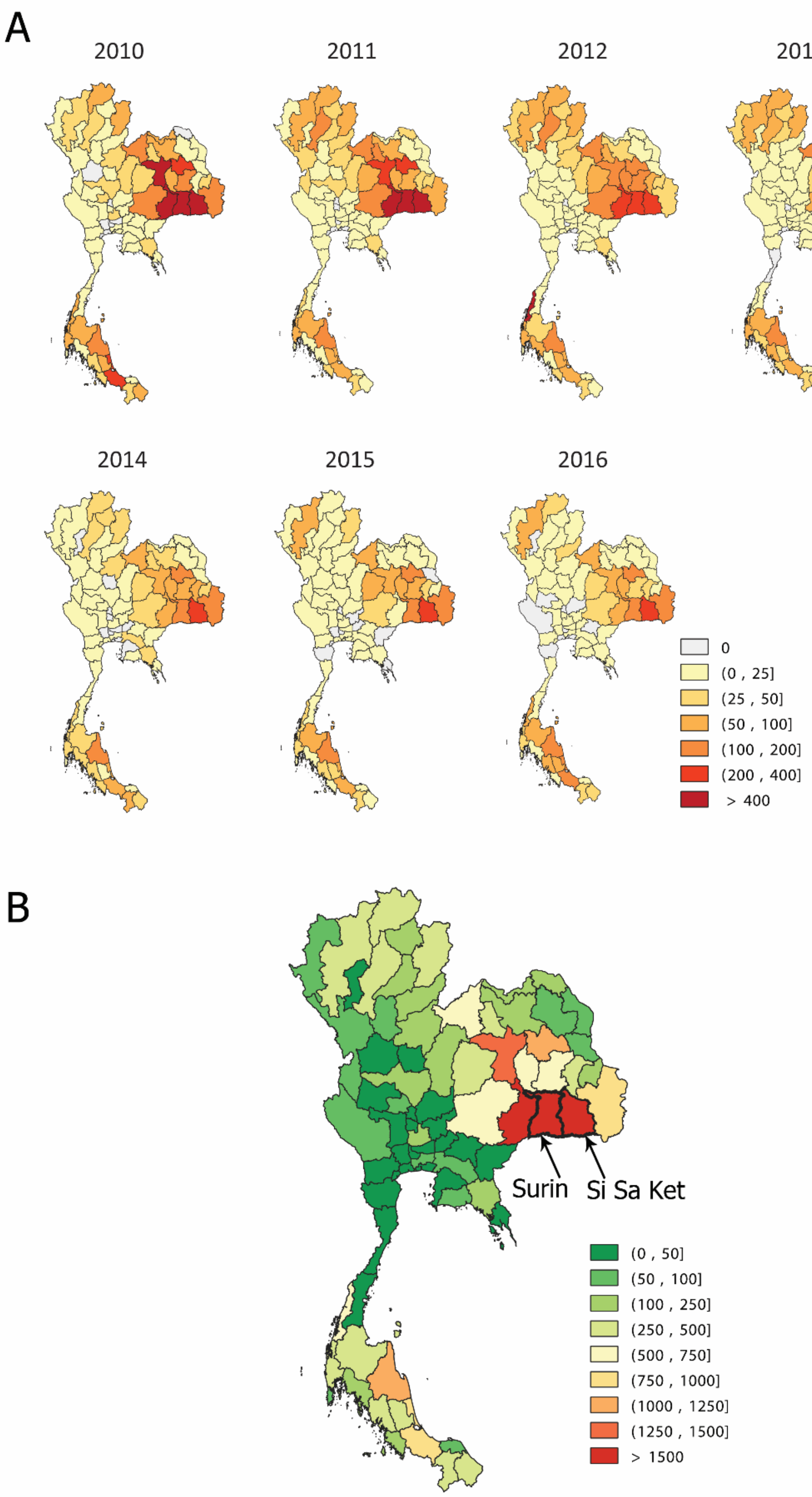

Figure 2. The map of reported cases in Thailand. The annual reported cases during 2010-2016 (A). The total reported cases during 2010-2016 (B).

Using the model described in the methods section, we fit eleven models (our ten models plus the null model) to the reported cases from 2010 to 2015 with time lags between 0-8 weeks for each province (Fig. 3). In general, we found that model 1 (M1) improved the fit, which indicated that making the transmission rate a linear function with environmental variables has an important impact on the infection dynamics in humans. Comparing the models incorporating flooding or rainfall factors (M1-F and M1-R), we found the model including the flooding factor fit better. The models that also included a temperature effect showed better performance. Overall, the model with the transmission rate dependent on flooding and temperature (M1-FT) had the lowest negative log-likelihood. Thus, we selected the M1-FT as the best-fit model for further analysis. The log-likelihood value of M1-FT varied time lags of flooding showed a similar pattern, which has a high value for time lag around one month (Fig. S2.). The effect of time lag on the temperature was found to be different than the time lag associated with flooding. The results indicate that the transmission dynamics depend on the weather in the given areas.

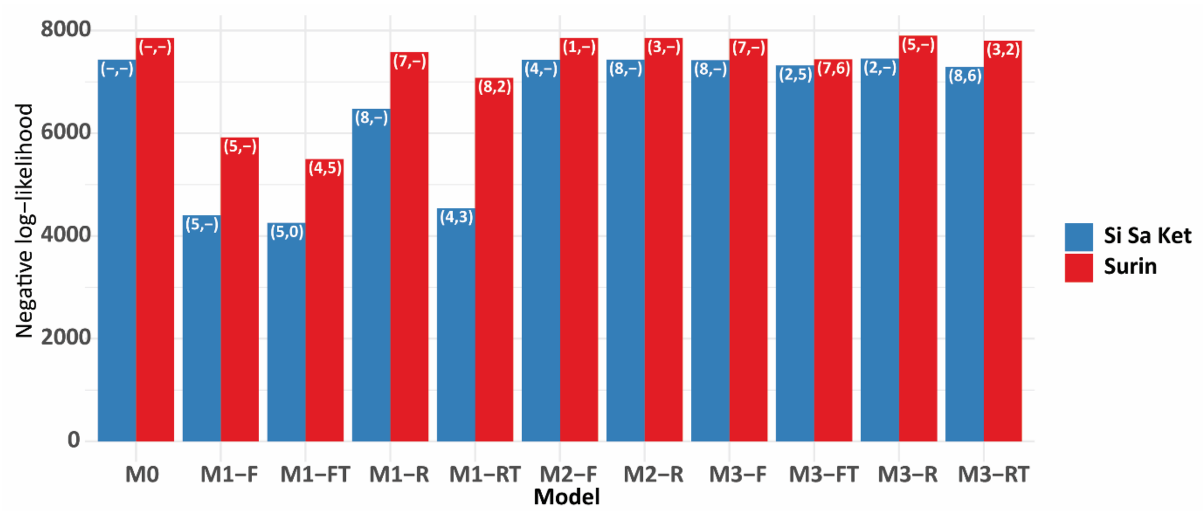

Figure 3. Bar chart of negative log-likelihood values for the ten models compared to a null model (M0) for the two provinces. The parentheses of each bar shows the time lag in week of flooding (rainfall) and temperature (t_1, t_2).

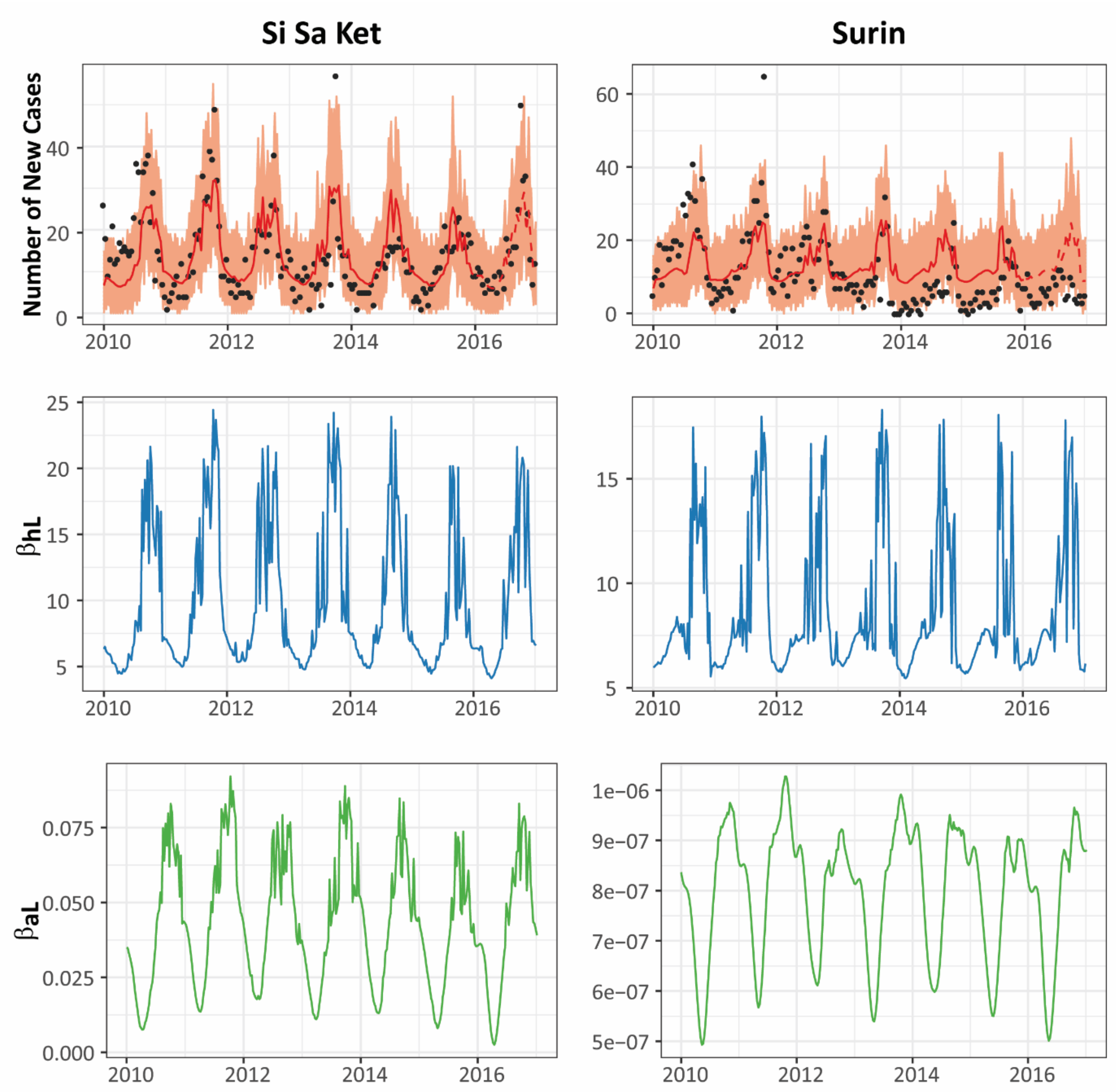

Figure 4. The fitted results of the M1-FT model (red line) compared to the reported cases of leptospirosis (black dot). The orange shaded area displays 1,000 curves of the stochastic simulations. The red dashed line represents the predicted cases for 2016. The time-dependent transmission rate from the contaminated environment to susceptible human and susceptible livestock (β_{hL} and β_{aL}) correspond to values in Table S1 are shown in the blue and green lines, respectively.

The M1-FT fitting and the stochastic simulation results, using the parameters shown in Table S1, are shown in Fig. 4. The stochastic output captures well the reported data. These results provide a reasonable fit with the predicted cases for 2016. Our model can provide more understanding on the transmission dynamics in contaminated environments.

The transmission rate from the contaminated environment to humans and livestock is plotted versus time according to the flooding and temperature factors (Fig. 4). The average transmission rate from the contaminated environment to humans (β_{hL}) over time is 9.886 and 8.737 for Si Sa Ket and Surin. This corresponds to a decline in the total number of reported cases during the dry season. The transmission rate from the contaminated environment to livestock (β_{aL}) also varied with time. It was higher in Si Sa Ket and lower in Surin. However, the β_{hL} was always the highest transmission rate. This result indicated that the main reason for human infection is due to the transmission of leptospires from the contaminated environment, rather than from contact with infected animals. Comparing the coefficients of β_{hL}, the flooding indicator had the most impact on transmission, which indicates a high amount of flooded area leads to higher cases.

The fitting results indicate that our model is capable to reproduce the incidences of the leptospirosis epidemic, using the seasonal changes of the amount of flooded area as an indicator of increased infection rates. The number of new infection cases can be predicted during winter, depending on the parameters calculated in the given areas.

In this work, we estimated the time-dependent reproduction number (R_{td}) for two provinces with the 95% confidence interval using the simulation results as shown in Fig. 5. We found the R_{td} oscillated around 1.0 which suggests it is an endemic disease, as expected for leptospirosis in Thailand. The mean (sd) of R_{td} is estimated at 1.020 (0.198) and 1.011 (0.158) for Si Sa Ket and Surin. A similar pattern of R_{td} was observed for both provinces in the same region in the simulated cases. Note that this estimation was based on the observed human cases. Normally, leptospirosis has a basic reproduction number close to zero due to its minimal transmissibility among human population. However, this estimation could provide a better picture of how leptospirosis transmits from animal sources and contaminated environments to humans.

Figure 5. The estimated R_{td} for the two provinces plotted with the 95% confidence interval.

As no vaccine or specific medicines are available for leptospirosis, the most important strategy to control the disease is to decrease the transmission rate. Figure 6 shows the PRCC values with 95% CI, obtained for the ten parameters in Table S1. Absolute PRCC values greater than 0.3 are considered important parameters. We found that the parameters of β_{hL} (h_1, h_2 and h_3) were the most important on the total number of cases for all provinces. Our results also suggest how decreasing the transmission rate of leptospirosis from the contaminated environment to human can affect the leptospirosis dynamics to reduce the number of human cases. Figure 7 shows how the number of human cases can be reduced as the transmission rate of β_{hL} is reduced. A 90% reduction ($0.9\beta_{hL}$) could reduce the total number of human cases by about 90%. Considering the overall results, this study suggests that we should avoid contacting contaminated environments during flooding.

The infection rate extrapolated from the parameters of Si Sa Ket were also calculated for 2016 in other providences of Thailand (Fig. S3.). Interestingly, we found that high infection rates were predicted in other regions rather than just the northeast. This may due to the high percentage of flooded areas observed in the other regions. Our results also suggest that the public health sector should increase awareness of outbreaks in these regions.

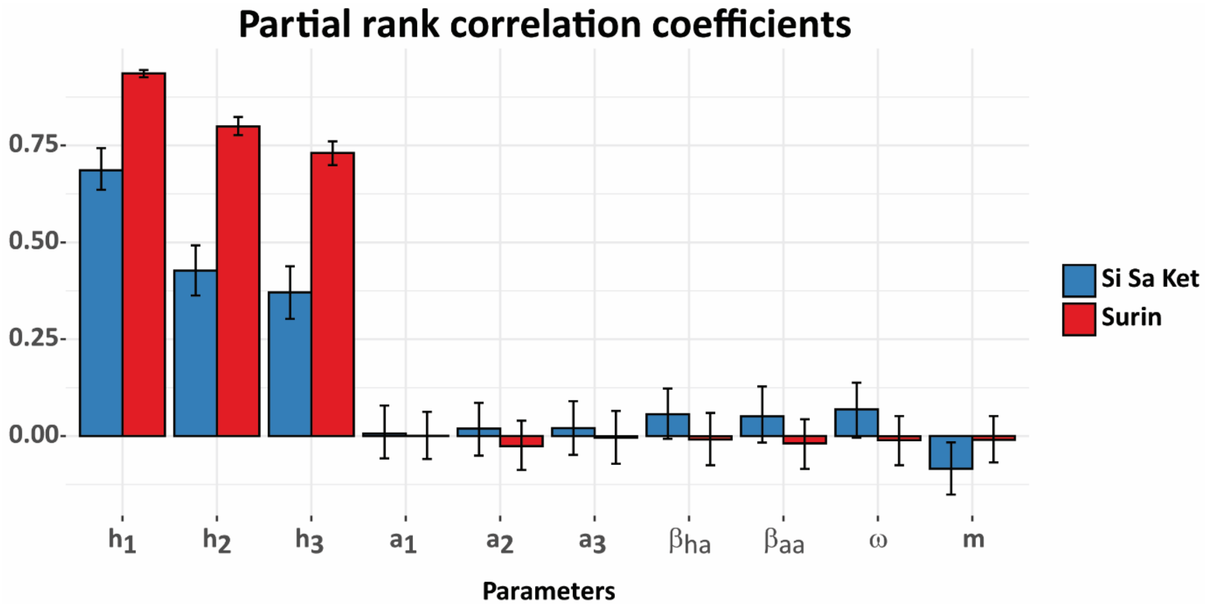

Figure 6. Partial rank correlation coefficients of the ten parameters and the total number of cases, plotted with an error bar showing the 95 % confidence interval. The h_i and a_i are constant values to calculate the transmission rates β_{hL} and β_{aL}, respectively.

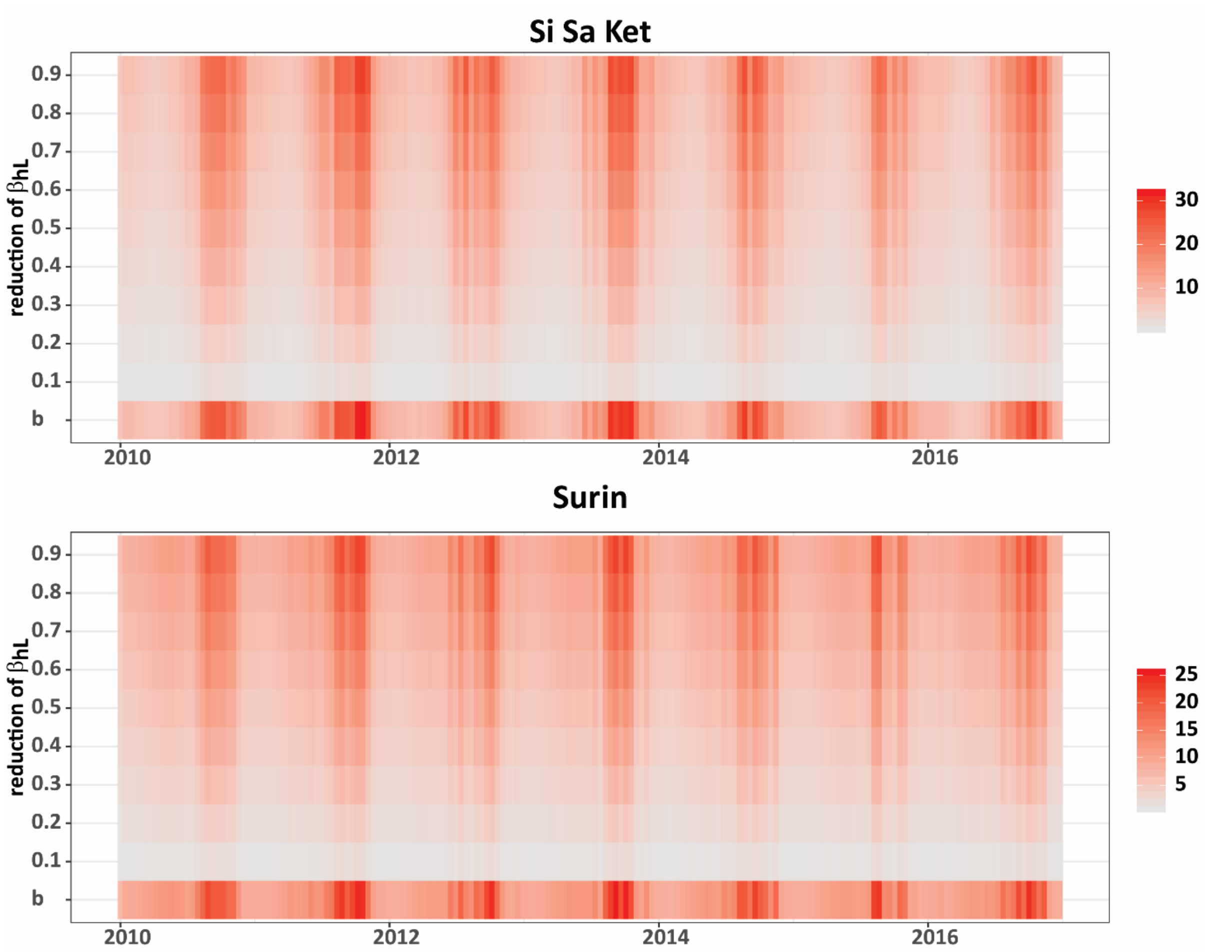

Figure 7. The number of human cases as the transmission rate from the contaminated environment to human (β_{hL}) of M1-FT is varied between $0.1\beta_{hL}$ to $0.9\beta_{hL}$, where b is the baseline.

Discussion

In this work, dynamical models, that include environmental data are presented and used to describe the transmission of leptospirosis in two provinces in the northeastern region of Thailand. This work presents the first attempt to incorporate environmental data into the mathematical models of leptospirosis transmission. The annual change of the environmental data can describe the seasonal epidemic with higher prevalence during the rainy season for the northeastern region, than a model not incorporating any environmental data.

Our finding suggests that transmission from a contaminated environment, as opposed direct contact with an infected animal, is the best model. This study is novel by finding that the amount of flooded area in a region, which obtained from a remotely sensed data, is the most important factor for leptospirosis transmission to humans. This implies that including a leptospires compartment, which refers to the number of pathogenic bacteria in the contaminated environment, reasonable describes the infection of humans during an endemic.

Previous studies have pointed out that leptospires survive and persist in the environment, both water and soil, for several weeks[49]. Environmental survival of pathogens can be an important parameter in epidemiology. During heavy rain with increased flooded areas, leptospires in the environment have more chances to enter the human body via cut skin. Working or living in flooded areas has been identified as a significant factor for increasing the contraction of leptospirosis[50]. Analysing our model, after fitting to human data from 2010-2015, the amount of flooded area was shown to be more important to improve the model as compared to the rainfall. Our results are consistent with a previous study that observed animals in Thailand from 2011–2013[21]. This indicates that flooding is a factor that influences the epidemiology of leptospirosis in both humans and animals. Flooding was also observed to be an important risk factor in other countries such as Argentina[51], Brazil[52] and Malaysia[53]. In our study, including the effect of temperature in the model improved the transmission model a modest amount. The temperature may affect leptospire virulence[38], and the transmission rate. The temperature effect observed in our study is in line with previous studies[54-56].

In this study, the time-dependent reproductive number was estimated for leptospirosis in humans. Normally, the basic reproductive number (R_0) cannot be estimated in humans due to minimal transmission between humans. However, in our case, we focused on how the transmission occurred in humans in term of R_{td}. Our model's estimation highlights that leptospirosis occurs mainly during mid-year for provinces in northeastern region.

From the PRCC analysis of our model, the transmission rate of leptospires to humans is most effected by the total number of cases. A disease control method, according to the PRCC results, suggest avoiding flooded areas, to reduce the transmission rate during an outbreak[57]. And protective equipment, such as wearing boots or gloves, is recommended when in contact with flooded areas.

Note that our proposed model is based on several assumptions, one of which is that the environmental parameters linearly affect the rates in the mathematical model. We do not consider other functions such as a Gaussian function due to the complexity. In general, models assume that the entire population is homogeneously mixed. The stochastic simulations in our results can estimate the fluctuations of the epidemic curve. Other animal, such as rodents, were not included due to the limitation of data on the rodent population. Rodents also carrying leptospires during the rainy period, and risk transferring the disease to humans[58]. Other factors such as human mobility, personal hygiene, and protective equipment, were also not accounted for in this study. The fitting process is done by only fitting to the reported data in humans, because of the limitation of livestock infection data. Another limitation we faced is on the National Surveillance System. Errors in the final model may be caused by underreported cases from the private health care centres, asymptomatic transmission, poor reporting to the National Surveillance System or the lack of leptospire data in the environment.

In summary, the leptospirosis transmission model predicts the significant environment factor associated with leptospirosis transmission is flooding. A reduction in contact with a contaminated environment can help to improve disease control. This work can be applied to other leptospirosis epidemic areas where flooding data is provided. Further studies should be carried out to access the role of livestock and other relevant data on the transmission of leptospires. Climate change or extreme weather events can also be modelled to predict the severity of future leptospirosis outbreaks[59]. Based on our results, public health policy maker may guide the people who work close to, or in contaminated environments to avoid potential sources of leptospirosis, or by protecting themselves by wearing boots to reduce the leptospirosis outbreak.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Contributions

SC: conceptualized, developed the model, performed the analysis, revising it critically for important content, wrote the first draft and wrote the manuscript. KCM: participated in its design, analysis and involved in drafting the manuscript. AW: participated in its design and involved in drafting the manuscript. CM: participated in its design, revising it critically for important content and wrote the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Impact of rainfall on the transmission of leptospirosis in Si Sa Ket, Thailand

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Abstract. Leptospirosis is a worldwide zoonotic disease, especially in tropical and sub-tropical countries. In Thailand during the rainy season, agricultural and livestock workers are the main occupational risk groups, who are likely to be in contact with the contaminated environment. In this work, we aimed to study the impact of rainfall on the transmission of leptospirosis using a stochastic cellular automata model in Si Sa Ket, Thailand, which has the highest reported cases from 2014 to 2018. Two bi-dimensional square lattices are created to represent human and contaminated environmental lattices. The reported cases are used to fit with the simulation results by varying the transmission probability. The transmission probability that depends on a sinusoidal function and the rainfall index were compared. This study highlighted that seasonal rainfall contributed to the transmission dynamics of leptospirosis. The total epidemic size, which is the sum of overtime cases, was investigated to find the critical transmission probability from endemic to epidemic state. Further study of other factors such as flooding and temperature, should be investigated for a better understanding of how the transmission of leptospirosis impacts the environment.

Introduction

Leptospirosis is an important bacterial zoonosis of worldwide and mostly affects tropical and subtropical countries [1, 2]. The disease is caused by pathogenic spirochete bacteria, genus *Leptospira* [3], which affects humans and animals. The transmission of this disease to humans or animals can occur by exposure to direct contact with infected animals or indirect via contaminated freshwater, soil, or mud [4]. Humans mostly infected by indirect exposure to a contaminated environment [5]. The time between exposure to symptoms and signs appearance (incubation period) of leptospirosis ranges from 7 to 12 days [4]. The acute phase is usually sudden and characterized by fever, headache and myalgia [5]. Later symptoms may include conjunctival injection, abdominal pain, vomiting, prostration, icterus, anuria or oliguria, cardiac arrhythmia or deficiency, meningeal syndrome and a skin rash [5].

In Thailand, the occupation of farmers and agricultural workers is important, estimated around 30% of the population in 2018 [6]. This occupation is the risk group, i.e., the agricultural workers usually walk barefoot in paddy fields lead to exposure with water for a long period, which may cause skin wounds and mucosae to provide routes of entry for leptospires into the body [7]. According to the epidemiology of leptospirosis, reported cases mostly found in rural areas than urban ones because of the environmental factors mentioned [8].

This bacteria can survive for days to months in water or soil [9, 10], which caused outbreaks occurred typically in the rainy season. Thus, the weather condition is one of the major factors influencing the spread of the bacteria [11]. In Salvador Brazil, the incidence of hospitalized leptospirosis patients was positively associated with increased rainfall [12]. The seasonal pattern of leptospirosis cases was observed along with the correlation of rainfall in India [13] and Sri Lanka [14].

Many studies have been proposed on leptospirosis mathematical models. Triampo et al. presented a mathematical model for the leptospirosis using the rate of transmission from an infected rat to a susceptible human varies with the amount of rainfall in Phrae and Nakhon Ratchasima Thailand [15]. They considered a number of leptospirosis cases in Thailand and shown their numerical simulations [16]. Zaman et al. presented an SIR model of human and vector (rat) population using the real data of Thailand for their numerical simulations [17]. Holt et al. used the SIR model to understand the behavior of infection in an African rodent of Tanzania [18]. Pongsumpun et al. developed the SIR-SI model to study the behavior of leptospirosis disease, represented the rate of change for both the vector (rat) and human population [19].

However, those of study did not consider in spatial aspect. The Stochastic Cellular Automata (SCA) is the model that used to describe the spatial dynamics, which are dynamical systems, discrete in space and time [20]. Each lattice of cell can assume a state in a finite set, which can change at every time step based on the transition rules and the state of cell or its neighbor. This model allows to study the environmental transmission for leptospirosis. Previously, Athithan presented a Cellular Automata based computational model for the spread of leptospirosis between human and animal using voting rules [21]. The simulation results are compared with the real data of leptospirosis infection in Thailand during 2000 and 2001. They found that the results were closely in match with the data. However due to the complexity of leptospirosis transmission, the environmental lattice should consider. The probability of changing status of human should depend weather condition and seasonal effect [13].

In this work, we developed the Stochastic Cellular Automata model using heterogeneous rules which consist of two bi-dimensional lattices, i.e., human and environmental lattices for leptospirosis transmission. We aimed to study the impact of transmission rate depends on the rainfall. The model was based on the rural shape of Si Sa Ket Thailand. In the model, we investigated the epidemic size to find the critical transmission probability from endemic to epidemic state.

Method

Data collection

In this study, we study the leptospirosis outbreak of Si Sa Ket Thailand. Data were collected from the national disease surveillance, Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand [22]. Data collection was performed as a part of routine clinical examination procedures.

The amount of daily rainfall for the duration of the study 2014–2018 was obtained from the real-time TRMM Multi-Satellite Precipitation Analysis [23]. We derived daily precipitation from 3B42RT. The daily accumulated precipitation is obtained from TRMM 3B42RT Daily [15, 24].

Model

The proposed SCA model is constructed based on the existing knowledge about leptospirosis transmission. There are two bi-dimensional square lattice size (1000×1000) where a cell is in position (i,j). The total population is assumed to be 350,000 individuals, who have agricultural and farmer worker at Si Sa Ket. Each individual (H_{ij}) is chosen randomly on a cell. Thus, human lattice will consist of occupation or empty site. Human individual can assume to be one of four states, which is in a susceptible state (S), an exposed state (E), an infectious state (I), and a recovered state (R) as illustrated in figure 1. The environment lattice can contain both empty sites and contaminated environment (representing the source of leptospirosis if infected), which estimated to 60% of lattice size as illustrated in figure 1. To simplify the model, we assumed that contaminated environment cell can transmit the infection to humans. In this model, we used the periodic boundary condition and take each time step to correspond to one day.

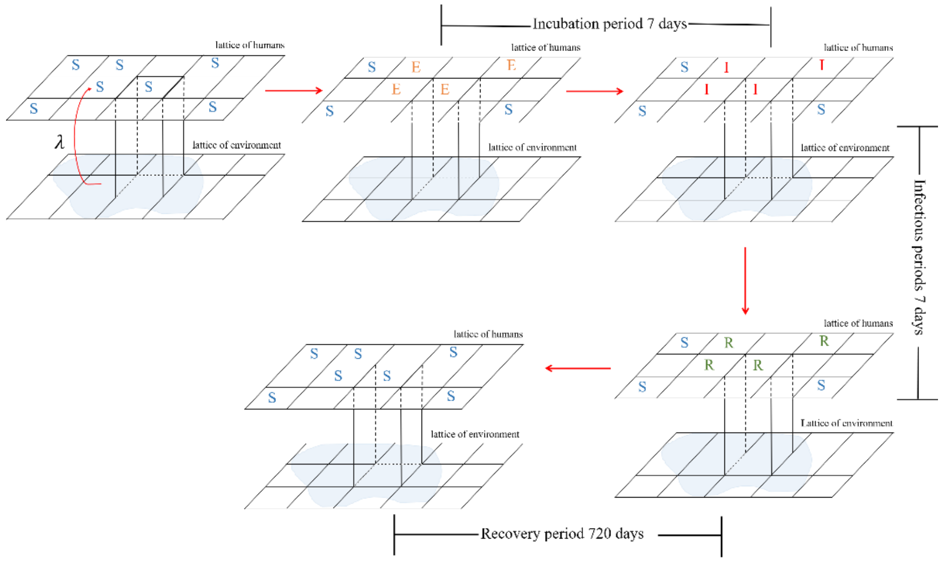

Figure 1. Schematic illustration of the transition state of the Stochastic Cellular Automata model.

In this work, we assumed humans individual, who are not infect with leptospires, randomly chosen move into empty site with probability ρ_{mob} = 0.5 [25] in each day. The length of human movement depends on the probability of the exponential step length, which is $P(r) = (r + \Delta r_0)^{-\beta} e^{-r/\kappa}$ with exponent β=1.75, Δr_0=1.5 km and cutoff values κ=80 km [26]. People can move within the maximum of half length (1000/2). The angle of movement is randomly chosen from a uniform distribution $[0, 2\pi]$. The parameters for the human population and mobility are shown in Table 1.

After human movement, if the position of the susceptible individual matches with the contaminated environment cell, the susceptible individual will gets infect with transmission rate (λ) to be exposed state. An exposed individual becomes an infected individual after a latent period of fixed length τ_E. An infected individual will infect for τ_I period then become a recovered state. This recovered individual will become an again susceptible period of fixed length τ_R.

To study the impact of rainfall, the transmission rate depends on the rainfall index ($R(t)$) as in equation (1) compared to null hypothesis as a sinusoidal function (equation (2)). The transmission rate (λ) is assumed as a linear proportional of environmental variables to test different hypotheses given by:

$$\lambda_1(t) = n_0 + n_1(R(t) - \tau) \tag{1}$$

$$\lambda_2(t) = n_0 + n_1(1 + \sin(2\pi t/365) - \tau) \tag{2}$$

where n_0 and n_1 are constant values. The reported data during 2014 and 2018 is used to fit with the simulation results. The parameters n_0 and n_1 were chosen, where the Mean Square Error (MSE) is minimized.

Table 1. Parameters for human and environmental lattices.

Description	Symbol	Values
Human population size	N_H	350,000
Daily rate of human mobility	ρ_{mob}	0.5 [25]
Water area density in environmental lattice	ρ_E	0.6
Incubation period for human	τ_E	7 days [4]
Duration of infection for human	τ_I	7 days [4]
Duration of loss immunity for human	τ_R	720 days (estimated)

Result /discussion

In this work, we aimed to study the impact of transmission rate depend on the rainfall index compared to sinusoidal function using the SCA model in Si Sa Ket, Thailand. We found the rainfall index more impact than sinusoidal function, which showed better fit with reported cases.

Figure 2 showed the relation between reported cases of leptospirosis, normalized rainfall index, and sinusoidal function. The number of reported cases all year round showed a seasonality pattern. The peak of leptospirosis curve occurred between August and October correspond to the rainy season. We found the peak of reported cases correspond to the peak of rainfall index and sinusoidal curve.

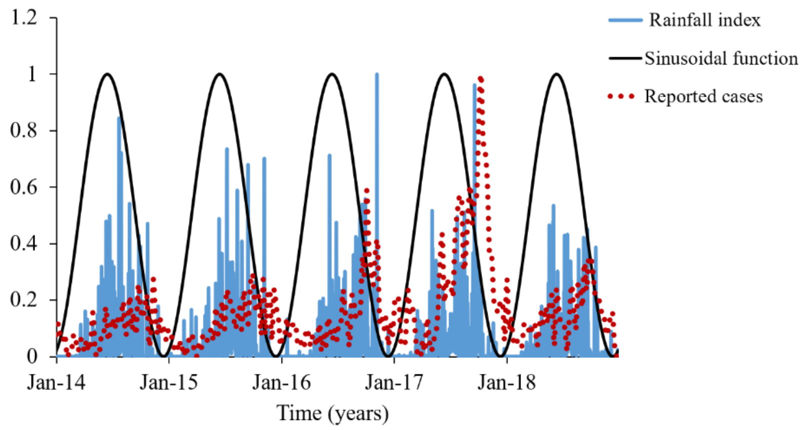

Figure 2. The relation between reported cases of leptospirosis, normalization rainfall index and the sinusoidal function for 2014-2018.

We varied time lag of the sinusoidal function, found that time lag of 4 weeks consistent with reports cases. We compared the real data and simulation results using mean square error (MSE), which found the minimized of MSE equal to 64.30 (figure 3). However, this function captured the reported cases only for the small value. The simulation result of the transmission rate depends on rainfall index with the associations observed at time lag of 2 weeks, which correspond to previous study [27]. The peak of leptospirosis cases corresponds with the peak of simulation results in almost every year. However, it could not describe the data on 2017 due to the other factor such as monsoon and heavy rainfall [28]. In fitting process, our results suggested that using rainfall index fit better than a sinusoidal function, which found MSE equal to 47.35. This finding indicate that the rainfall index contributed to the transmission dynamics of leptospirosis. Although, the sinusoidal function has been commonly used to represent seasonality in epidemic models [29].

The epidemic of leptospirosis are known to be a seasonal pattern. Rainfall is an important risk factor for leptospirosis outbreaks and strongly associated with the tropical settings [30-32]. The heavy rainfall washes superficial soils, bringing pathogenic leptospires in freshwater bodies, where humans will be exposed. Massive leptospirosis outbreaks usually emerge following waterlogging. After heavy rainfall, this pathogen can survive for days to months in a contaminated environment [33].

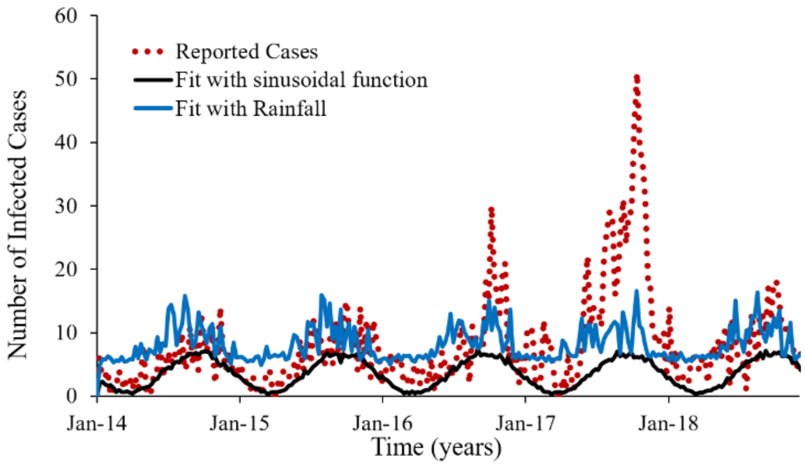

Figure 3. The reported cases of leptospirosis and the simulation result prediction of the transmission depend on the sinusoidal function $n_0 = 3.47 \times 10^{-7}$ $n_1 = 2.09 \times 10^{-6}$ and the rainfall index $n_0 = 4.01 \times 10^{-6}$ and $n_1 = 3.21 \times 10^{-5}$.

In various types of epidemic models, it has been the central issue of how the final epidemic size is determined by the individual system parameters or the composite of them [34]. In this study, we defined the final epidemic size as the fraction of recovered at steady state. To investigate the transmission rate contributes to the final epidemic size in our model, we set the transmission rate be a constant value ($\lambda = n_0$). The critical transmission rate is showed in figure 3, suggests that point transition from endemic phase to epidemic state.

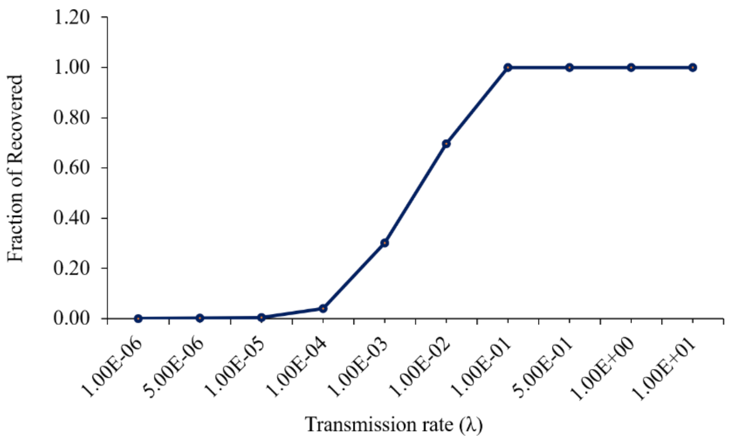

Figure 3. The final epidemic size as predicted by the SEIR model is shown with respect to the transmission rate $\lambda = 1 \times 10^{-6} - 1 \times 10^{1}$.

In conclusion, our results highlighted that the transmission rate depends on rainfall index with time lag 2 weeks capture has impact on the leptospirosis outbreak in Si Sa Ket. We also find the critical transmission rate, which can be basic idea to control the outbreak. However, there are several factors could influence to leptospirosis such as flooding, temperature and humidity. Further study of other factors should be investigated for a better understanding of how the transmission of leptospirosis impacts the environment.

Acknowledgments

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