Science of the Total Environment 832 (2022) 155018

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Unraveling the invisible leptospirosis in mainland Southeast Asia and its fate under climate change

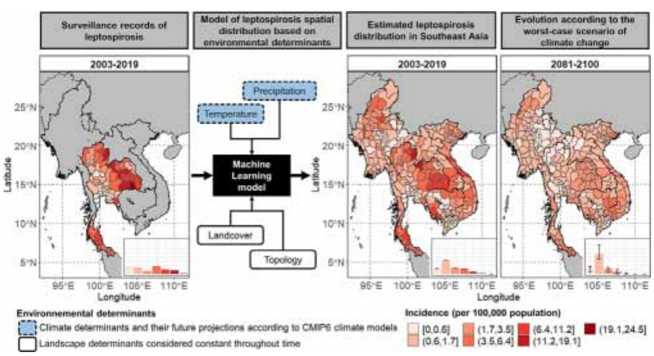
Léa Douchet [a,b,*], Cyrille Goarant [c], Morgan Mangeas [a], Christophe Menkes [a], Soawapak Hinjoy [d], Vincent Herbreteau [b]

[a] ENTROPIE, IRD, Univ Reunion, CNRS, IFREMER, Univ Nouvelle Calédonie, 101 Promenade Roger Laroque, Nouméa 98800, New Caledonia
[b] ESPACE-DEV, IRD, Univ Montpellier, Univ. Antilles, Univ Guyane, Univ Réunion, 5 Preah Monivong Blvd, Phnom Penh 12201, Cambodia
[c] Institut Pasteur in New Caledonia, Institut Pasteur International Network, Leptospirosis Research and Expertise Unit, 9 Ave Paul Doumer, Nouméa 98800, New Caledonia
[d] Office of International Cooperation, Department of Disease Control, Ministry of Public Health, 88/21 Tiwanon Road, Thaladkwan, Muang, Nonthaburi 11000, Thailand

HIGHLIGHTS

- Despite its high burden, leptospirosis remains poorly documented in Southeast Asia.
- Leptospirosis regional burden can be modelled with environmental determinants.
- The spatial distribution of its incidence is heterogeneous in Southeast Asia.
- Climate change would induce a global decline in incidence with regional contrasts.
- Future socio-economic and behavioral changes could impact these forecasts.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Scott Sheridan

Keywords:
Waterborne
Zoonosis
Spatial modelling
Environment
Global change
Regional scale

ABSTRACT

Leptospirosis is a neglected waterborne zoonosis of growing concern in tropical and low-income regions. Endemic in Southeast Asia, its distribution and environmental factors such as climate controlling its dynamics remain poorly documented. In this paper, we investigate for the first time the current and future leptospirosis burden at a local scale in mainland Southeast Asia. We adjusted machine-learning models on incidence reports from the Thai surveillance system to identify environmental determinants of leptospirosis. The explanatory variables tested in our models included climate, topographic, land cover and soil variables. The model performing the best in cross-validation was used to estimate the current incidence regionally in Thailand, Myanmar, Cambodia, Vietnam and Laos. It then allowed to predict the spatial distribution of leptospirosis future burden from 2021 to 2100 based on an ensemble of CMIP6 climate model projections and 4 Shared Socio-economics Pathways ranging from the most optimistic to the no-climate policy outcomes (SSP1–2.6, SSP2–4.5, SSP3–7.0 and SSP5–8.5). Leptospirosis incidence was best estimated by 10 environmental variables: four landscape-, four rainfall-, two temperature-related variables. Of all tested scenario, the worst-case scenario of climate change (SSP5–8.5) surprisingly appeared as the best-case scenario for the future of leptospirosis since it would induce a significant global decline in disease incidence in Southeast Asia mainly driven by the increasing temperatures. These global patterns are however contrasted regionally with some regions showing increased incidence in the future. Our work highlights climate and the environment as major drivers of leptospirosis incidence in Southeast Asia. Applying our model to regions where leptospirosis is not routinely monitored suggests an overlooked burden in the region. As our model focuses on leptospirosis responses to environmental drivers only, some other factors, such as poverty, lifestyle or behavioral changes, could further influence these estimated future patterns.

* Corresponding author.
E-mail address: lea.douchet@ird.fr (L. Douchet).

http://dx.doi.org/10.1016/j.scitotenv.2022.155018
Received 14 December 2021; Received in revised form 16 March 2022; Accepted 30 March 2022
Available online 4 April 2022

1. Introduction

Leptospirosis, a bacterial disease caused by spirochetes of the genus *Leptospira*, is an emerging public health concern (Costa et al., 2015). This neglected zoonotic disease (Goarant et al., 2019) with a global distribution affects more than 1 million persons yearly worldwide, killing 58,900 (Costa et al., 2015). Human infection often shows minimal or no clinical manifestation. Patients seeking medical attention usually develop an acute, undifferentiated febrile illness difficult to diagnose clinically (Goarant, 2016). Left untreated, leptospirosis can drift to severe and potentially fatal Weil's disease with liver damage, kidney failure or an often-fatal severe pulmonary hemorrhage (Bharti et al., 2003).

Pathogenic leptospires live in the kidney tubules of mammals including rats, livestock and domestic pets that act as reservoirs (Bharti et al., 2003). Once shed in the urine, they can survive into the water and soil environment for weeks to months (Bierque et al., 2020). Human infection occurs through contact with contaminated water or soil, less frequently through direct exposure to an infected animal. Leptospirosis has a low incidence in temperate climate, the greatest concerns arise in tropical and subtropical areas, especially in developing countries where conditions are suitable for leptospires persistence into the environment and contact with populations (Bharti et al., 2003).

The infection results from a combination of environmental factors that affect both the survival of leptospires in the environment and human exposure. Leptospirosis is affected by climate conditions, especially under tropical climate with more extreme events. Heavy rainfall and flooding are the most cited environmental determinants of seasonality (Tangkanakul et al., 2005; Wuthiekanun et al., 2007) and outbreaks (Amilasan et al., 2012; Kawaguchi et al., 2008; Thaipadungpanit, 2007; Togami et al., 2018) of leptospirosis, since such climatic events are prone to bring contaminated waters and reservoir animals closer to humans. Temperature is also considered an important risk factor (Levett, 2001). In New Caledonia, hot and rainy environments favor leptospirosis outbreak, seasonally by increasing rodent population and leptospirosis carriage (Pérez et al., 2016) and inter-annually during La Niña phases of the ENSO (El Niño Southern Oscillation) (Weinberger et al., 2014). Warm weather is also likely to increase human exposure by encouraging water-based activities and constraining humans and animals along the same water bodies (Lau et al., 2010; Narkkul et al., 2021). Many geographic and environmental patterns have been linked to human leptospirosis: agricultural areas at lower altitude in American Samoa (Lau et al., 2012), flood-prone areas in Brazil (Gracie et al., 2014), rivers and flood-prone rice fields in Thailand (Della Rossa et al., 2016), areas with higher forest coverage, permanent crops and secondary vegetation in Colombia (Gutiérrez et al., 2019) and area with favorable soil characteristics as moisture (Baquero and Machado, 2018; Cucchi et al., 2019), texture (Lau et al., 2012; Rood et al., 2017) and composition (Schneider et al., 2015, Schneider et al., 2012).

Southeast Asia is a region where leptospirosis is endemic with estimated high incidence (Costa et al., 2015). Human infections and outbreaks have been reported in Thailand (MoPH and Bureau of Epidemiology, 2020; Thaipadungpanit, 2007; Wuthiekanun et al., 2007), Laos (Kawaguchi et al., 2008; Laras et al., 2002; Mayxay et al., 2015), Vietnam (Laras et al., 2002; Van et al., 1998) and Cambodia (Berlioz-Arthaud et al., 2010; Hem et al., 2016; Laras et al., 2002; Seng et al., 2007). Few cases have been diagnosed in Myanmar except in Yangon (Dhawan et al., 2021) and at the Thai-Myanmar border (Ellis et al., 2006). Only Thailand systematically reports cases diagnosed throughout the country. Exposure is mainly occupational (Suwanpakdee et al., 2015) in agricultural workers, especially rice farmers (Tangkanakul et al., 2000; Watt et al., 2003). Because of the difficult clinical diagnosis and infrequent laboratory confirmation (Victoriano et al., 2009), leptospirosis remains under-reported in several countries and its regional distribution suffers major knowledge gaps (Costa et al., 2015). Southeast Asia experiences recurrent flooding, intense rainfall and hot temperatures, all expected to increase in both intensity and frequency with climate change (Field and Barros, 2014). Such extreme weather events could impact the distribution and extent of leptospirosis (Lau et al., 2010; Tabucanon et al., 2021), especially in the numerous population engaged in agriculture.

Proper estimates of leptospirosis distribution at local scale are essential to inform local decision-making and policy, and promote community awareness. Effective surveillance networks might be expensive to settle especially in areas facing development challenges as Southeast Asia. Additionally, estimating the leptospirosis near-future evolution within this climate-vulnerable area would help public health preparedness and assist in designing adaptation and mitigation strategies. Ecological models could typically inform on the spatiotemporal dynamics of the leptospirosis risk. Few studies have used spatial modelling to identify the local environmental determinants of leptospirosis infection in Thailand (Chadsuthi et al., 2021, Chadsuthi et al., 2012; Della Rossa et al., 2016; Suwanpakdee et al., 2015) and Cambodia (Ledien et al., 2017). Identification of key environmental factors has, however, been shown to strongly depend on the geographical scale used in modelling (Gracie et al., 2014) and on ecological settings (Lau et al., 2010). At present, explicit spatial models of leptospirosis are lacking in Southeast Asia, as are estimations of the responses of the disease distribution to climate change.

The goals of the present study are to (i) investigate the environmental factors driving leptospirosis at provincial level in Thailand where surveillance data is available and (ii) estimate leptospirosis distribution and near-future evolution in Thailand and neighboring mainland countries of Myanmar, Laos, Vietnam and Cambodia. We used leptospirosis surveillance data from Thailand spanning 17 years, where the disease benefited a structured surveillance system. Support Vector Regression modelling allowed identifying the climatic and environmental determinants of leptospirosis incidence spatially. We then extended the best model to Southeast Asia to produce maps of disease incidence under the present climate. That suggested a massive burden of leptospirosis in regions where the disease is not yet reported. Lastly, we used climate projections from CMIP6 model-based surface climates (Fick and Hijmans, 2017) to evaluate the future burden, predicting spatial heterogeneity in the future burden under different climate scenarios for the next 80 years.

2. Methods

2.1. Study site

The study was conducted in continental Southeast Asia and included the countries of Myanmar, Thailand, Lao PDR, Cambodia and Vietnam (Fig. 1). This region is composed of high mountains, plains and plateaus and is crossed by major river systems (from West to East: the Irrawaddy, Salween, Chao Phraya, Mekong and Red rivers). High mountains cover the north of the area, especially the northeast of Myanmar and the north of Laos. Mountainous chains extend toward the south along with the Thai-Myanmar border and the Laos-Vietnam border (Supplementary Fig. S1.). Irrigated plains and plateaus, mostly located in the south of the area, gather the most intensive agricultural activities, mostly rice cultivation. The climate of the region is tropical-hot and humid with two main seasons, the dry and the rainy season (Supplementary Fig. S2. and S3.). Recurrent and heavy rainfall occur during the monsoon. A third season with cooler weather is observed in the north of the area and in mountainous part of Myanmar and Laos. The study area was divided into 262 geographical units of analysis based on the administrative divisions of each country. We used the district level for Myanmar (80 districts) and the provincial level for Cambodia (25 provinces), Lao PDR (18 provinces), Thailand (76 provinces) and Vietnam (63 provinces), so that the units of analysis have similar areas.

2.2. Leptospirosis cases

The Bureau of Epidemiology of the Ministry of Public Health of Thailand (MoPH and Bureau of Epidemiology, 2020) provided monthly reported cases of leptospirosis per province from 2003 to 2019. This data includes both clinically diagnosed cases and a smaller number of

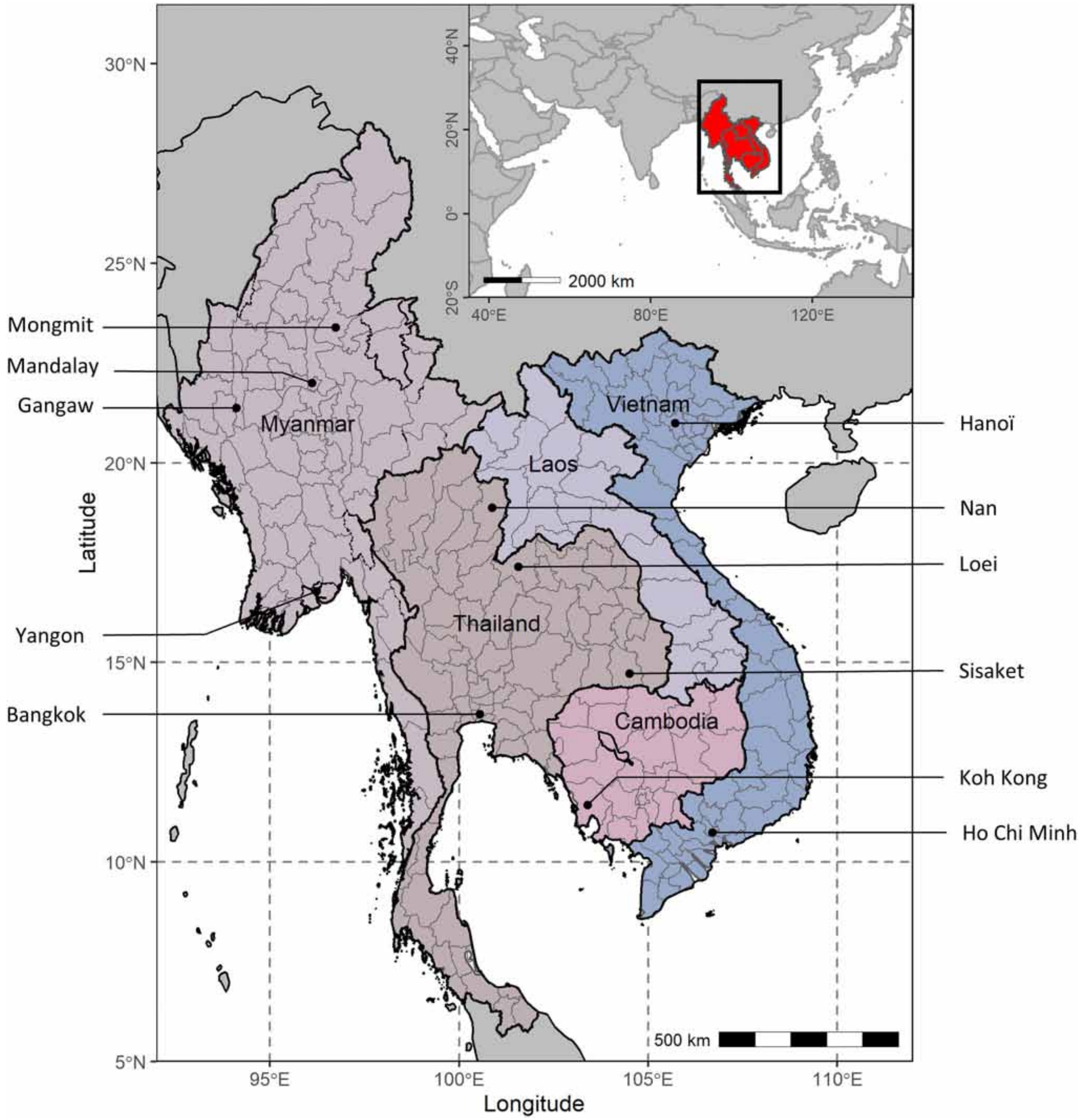


Fig. 1. Southeast Asia study area.

laboratory-confirmed cases. We calculated yearly incidence rate for 100,000 inhabitants using yearly population time series by province from the Department of Provincial Administration of Thailand. In 2011, Nong Khai (close to the Laotian capital of Vientiane) was divided in two to create Bueng Khan, the 77th province of Thailand. For the analyses, we aggregated the values of Nong Khai and Bueng Khan after 2011 to keep the number of provinces constant. We used the median of the yearly incidence rates time series for the period 2003–2019 as an indicator of the spatial distribution of leptospirosis.

2.3. Environmental data

Landscape, topographic and climate variables, expected to be involved into the leptospirosis transmission from known exposure risk factors (Mwachui et al., 2015), were retrieved from public databases (Table 1). We prepared spatial data and conducted statistical analyses with R (http://www.r-project.org/) and raster (Hijmans et al., 2015) and sf (Pebesma, 2018) packages.

We retrieved land cover information from the Regional Land Cover Monitoring System (https://landcovermapping.org) developed by SERVIR-Mekong. We used the 2018 dataset produced by the analysis of Landsat satellite images at a spatial resolution of 30 m. We calculated the percentage of coverage of each study unit (either province or district) for three variables of interest: 1) the cropland that includes the land cover classification of Orchard or plantation forest, Cropland and Rice, 2) the forest composed of flooded forest, forest, evergreen broad-leaf and mixed forest land and, 3) the urban and built-up classes. The coverage of soil texture, classified into 7 levels: coarse, medium, medium fine, fine, very fine,

Table 1
Descriptions of the variables used in the model.

Variables	Description (units)	Source
Time-series data[a]		
Precipitation		
Mean precipitation[b]	Mean monthly rainfall (mm)	Gridded monthly cumulated precipitation retrieved from Worldclim (Fick and Hijmans, 2017) database for the period 2003–2018 with a resolution of 2.5 min.
Variance of precipitation[b]	Inter-monthly variance of monthly rainfall (mm)	
Wettest quarter[b]	Mean precipitation of the wettest 3-months (mm)	
Daily cumulated rainfall		
Number of rainy days	Mean number of days with cumulated rainfall > 30 mm (days)	Gridded daily precipitations retrieved from TRMM (Huffman and Bolvin, 2013) for the period 2003–2019 at a resolution of 0.25°.
Temperature		
Maximum temperature (T_{max})[b]	Mean of the monthly maximum temperature (°C)	Gridded data of monthly maximum temperature and minimum temperature retrieved from the Worldclim (Fick and Hijmans, 2017) database for the period 2003–2018 with a resolution of 2.5 min.
Minimum temperature (T_{min})[b]	Mean of the monthly minimum temperature (°C)	
Range of temperature (T_{range})[b]	Mean of the monthly [$T_{max} - T_{min}$] (°C)	
Average temperature ($T_{average}$)[b]	Mean of the monthly [($T_{max} + T_{min}$)/2] (°C)	
Variance of T_{max}[b]	Inter-monthly variance of T_{max} (°C)	
Variance of T_{min}[b]	Inter-monthly variance of T_{min} (°C)	
Variance of *Trange*[b]	Inter-monthly variance of T_{range} (°C)	
Variance of *Taverage*[b]	Inter-monthly variance of $T_{average}$ (°C)	
Hottest quarter[b]	Mean T_{max} of the hottest 3-months (°C)	
Warmest quarter[b]	Mean $T_{average}$ of the warmest 3-months (°C)	
Surface runoff		
Surface runoff	Mean of monthly surface runoff (mm)	Gridded monthly surface runoff retrieved from the ERA5 (Hersbach et al., 2019) database for the period 2003–2018 with a resolution of 30 m.
Variance of surface runoff	Inter-monthly variance of surface runoff (mm)	
Cross-sectional data		
Soil type		
Coarse soil type	Coverage of soil texture (%)	Gridded data of soil texture classification retrieved from the ERA5 (Hersbach et al., 2019) database at a resolution of 30 km.
Medium soil type		
Medium fine soil type		
Fine soil type		
Land cover		
Cropland area	Coverage of orchard or plantation forest, cropland and rice lands (%)	Gridded data of land cover retrieved from the Regional Land Cover Monitoring System (RLCMS: https://landcovermapping.org) developed by SERVIR-Mekong for the year 2018 at a resolution of 30 m.
Forest area	Coverage of flooded forest, forest, evergreen broad-leaf and mixed forest lands (%)	
Urban area	Coverage of the urban and built land (%)	
Water occurrence		
Dry area	Coverage of water occurrence of 0% (%)	Gridded data retrieved from the Global Surface Water (Pekel et al., 2016) database of the frequency (between 0% and 100%) with which water was present on the surface between 1984 and 2019 at a resolution of 30 m.
Floodable area	Coverage of water occurrence between 0 + % and 93% (%)	
Permanent water surface	Coverage of water occurrence higher than 93% (%)	
Topography		
Mean elevation	Mean elevation of province (m)	Gridded data of elevation provided by SRTM (Farr et al., 2007) at a resolution of 90 m.
Mean slope	Mean slope in the province (no units) Spatial	The gridded tangent slope was computed using the 8 neighboring cells
Variance of slope	variance of slope (no units)	

[a] The raster resolutions of time-serie data were reduced to the province scale by averaging cells values at each time. Mean, variance and quarter values refers to temporal aggregates.
[b] Climate variables projected by 7 climatic models of the CMIP6 for 4 future periods 2021–2040,2041–2060, 2061–2080 and 2081–2100.

organic and tropical organic, and derived from the FAO/UNESCO Digital Soil Map of the World, was retrieved from the ERA5 dataset of Copernicus Climate Change Service (C3S) (Hersbach et al., 2019) at a grid resolution of 30 km. Only the coarse, medium, medium-fine and fine soil textures were found in the Thailand area and tested as variables for leptospirosis modelling. We retrieved the surface water occurrence at 30-meter resolution from the global surface water database (Pekel et al., 2016) (https://global-surface-water.appspot.com/). This dataset draws the frequency with which the water has been present over the area during the periods 1984–2019. We used it to estimate the coverage of each province that can potentially be flooded. We reclassified the occurrence value, expressed as a discrete percent, into three distinct classes (Supplementary Fig. S4.): dry area (occurrence of 0%), floodable area (occurrence between 1% and 93%) and permanent water surface (occurrence above 93%).

Topographic data were retrieved from the Shuttle Radar Topography Mission (Farr et al., 2007) (SRTM) Digital Elevation Model (DEM) with a spatial resolution of 90 m. We used this dataset to compute the mean elevation (in meters), the mean slope (in percentage) and the variance of slope (in percentage) in each province.

Time-series of monthly rainfall (mm), minimum temperature (T_{min}, °C) and maximum temperature (T_{max}, °C) from 2003 to 2018 were retrieved from the CRU-TS 4.03 (Harris et al., 2014) downscaled with WorldClim 2.1 (Fick and Hijmans, 2017) dataset at a grid resolution of 2.5 arc minutes (~4.1 km in the North and ~ 4.6 km in the South of the study area). We computed two other time-series based on these climate data: the average temperature ($T_{average} = (T_{max} + T_{min}) / 2$) and the diurnal range of temperature ($T_{range} = T_{max} - T_{min}$). For this same period, C3S ERA5 dataset (Hersbach et al., 2019) provided monthly data of surface runoff (resolution of 30 km), *i.e.* the amount of water that drains away over the surface modelled by considering rainfalls and the soil ability to retain water. These time-series data, provided as a raster were transformed spatially and temporally into climate indicators at the province scale with the following process:

1. we aggregated raster values spatially by computing the average of raster cell's value over each province,
2. we used these values, averaged at province scale, to compute the yearly evolution of climate data, computed for each province by averaging the values of each month across the years,
3. we computed a) the mean values, b) the variances of the yearly dynamic for each province and c) the mean rainfall of wettest quarter (mean precipitations of the 3 months with highest rainfall levels) and the mean temperature of hottest quarter (mean of the 3 months with highest T_{max}). We used these variables into the model to respectively describe

the distribution among provinces, the inter-monthly variability and the seasonal variability.

Finally, the mean yearly number of rainy days, defined as days with more than 30 mm precipitation, was extracted from the daily levels of precipitations available in the daily Tropical Rainfall Measuring Mission (TRMM)-3B42 database (Huffman and Bolvin, 2013) at a resolution of 0.25°.

2.4. Model fitting and analysis

Support vector regression (SVR) models using the Gaussian Radial Basis function kernel were adjusted on the log-transformed incidence of Thai provinces. We explored a large number of models with simulating annealing algorithm to define the number and combination of explanatory variables providing the best balance between parsimony and accuracy (Supplementary Fig. S5.). We used the mean squared error computed with leave-one-out cross validation (MSE_{LOO-CV}) as an indicator of the model accuracy to prevent overfitting. Finally, we retained the models providing the lowest MSE_{LOO-CV}, *i.e.,* the best predictive abilities. We adjusted the cost (C) and radial kernel's σ hyperparameters of the SVR model with grid searching to improve this predictive precision, *i.e.,* the $MSE_{LOO\text{-}CV}$.

We further explored the fitting of SVR to study the role of each identified environmental driver in the distribution of leptospirosis. We computed the importance score of variables, based on permutations processes repeated 1000 times. The loss in MSE induced by the dataset disruption was quantified relatively to the MSE from the non-permuted dataset with a ratio. The marginal effect of each variable on the incidence prediction was studied using Individual Conditional Expectancy (ICE) curves, *i.e.,* drawing the evolution of the predicted incidence in each province when one variable is changing. The partial dependence of each variable to the leptospirosis incidence was computed by taking the mean trend and the variance of these ICEs.

2.5. Estimation of leptospirosis distribution and evolution along with climate change

We used the best model to estimate the actual (2003–2019) spatial distribution of leptospirosis in continental southeast Asian countries showing environmental conditions similar to Thailand (Supplementary Fig. S6.): Myanmar, Laos, Cambodia and Vietnam. We forecast its mean evolution using the CMIP6 (Eyring et al., 2016) future climate projections from 6 global climate models (MIROC-ES2L, MIROC6, BCC-CSM2-MR, CNRM-CM6-1, CanESM5, IPSL-CM6A-LR) retrieved from the Worldclim database (https://worldclim.org/) at a resolution of 2.5 min of arc. We used 4 scenarios of climate change based on the Shared Socio-economic Pathways (SSP): SSP1-2.6 (the "so-called" most optimistic scenario, which limits warming below 2 °C), SSP2–4.5 (limits warming below 3 °C), SSP3-7.0 (middle of the road) and SSP5-8.5 (the "so-called" worst-case scenario, which estimates the no-climate policy outcomes). Monthly averaged precipitation, maximum and minimum temperatures over four 20-year periods from 2021 to 2100 at a resolution of 2.5 min were used to compute the annual mean, the inter-monthly variance of precipitation, T_{max}, T_{min},T_{range} and $T_{average}$ for each period, similarly to step 3 in the section above describing the formatting of the historical data. The mean precipitation of the wettest quarter, averaged throughout each period, was also retrieved from the database and used in forecasting. The other features, for which no forecast was available, were considered constant, taken from the historical data to model the leptospirosis incidence. We retrieved the medium-variant projection of population at the country scale from the World Population Prospects, issued by the United Nations Population Division (United Nation, 2019). This projection estimates changes in fecundity and mortality based on the past experience of both the studied country and other countries sharing similar conditions. We averaged yearly population estimates over each studied period and computed a growth rate compared to the current period (2003–2019). The growth rate at the country scale was then applied to all provinces of the country.

The predicted incidences using each climate projection were then averaged under each scenario to observe the global trend of leptospirosis distribution. Provinces having similar dynamics of leptospirosis over time were classified into four groups using the K-means methods on the scaled (centered and reduced) incidence.

3. Results

3.1. Leptospirosis distribution in Thailand

The reported leptospirosis incidence in Thailand for the period 2003–2019 ranged from 0 to 24.5 cases per 100,000 population across provinces (median 5.2). The lowest incidence was in Samut Sakhon province (South-West of Bangkok) with a median of 0 (mean of 0.40) cases annually and the highest in Sisaket province (South of the northeastern region) with a median of 357 cases annually (Fig. 2, a). The province of Bangkok, the most densely populated, recorded a median of 8 cases annually (incidence of 0.14). The northeastern region gathered most of the highest incidence with 11 provinces recording incidence above 6.6 including Loei (incidence of 18.4, median of 113 cases annually) and Sisaket. The east of the North region also shows high incidence with Nan recording an incidence of 14.0 (median of 67 cases annually). South Thailand was the second region showing high incidence with in average (±S.E.) 7.01 ± 4.81, whereas the Central region recorded lower incidence (0.83 ± 1.37).

3.2. A regional model of leptospirosis driven by environmental determinants

Our SVR model, validated in leave-one-out cross-validation (MSE_{LOO-cv} = 0.19), accurately predicted the distribution of leptospirosis with a correlation of 0.88 between the observed and the predicted incidence (Fig. 2). The low incidence in the Central region and the higher incidence in the South and in the north-northeastern area were well predicted. Highest incidence tended however to be underestimated with the maximum predicted incidence being 16.5 per 100,000 population (Ranong province) while observed incidence was between 16.7 and 24.5 in 4 provinces (Ranong and 3 in the northeastern region, Fig. 2, c).

The exploration of a great number of models helped identifying the most robust determinants of leptospirosis. We identified 10 major variables (see Supplementary Figs. S1., S2. and S3.), out of the 29 tested, as key drivers for leptospirosis distribution (Fig. 3 and Supplementary Fig. S5.). Rainfall played a central role in the modelled distribution with 4 precipitation-based variables in the best model. The mean rainfall of the wettest quarter was found to be a major explanatory variable: leptospirosis incidence increased with higher levels of rainfall during the wettest 4-month period and reached a maximum with an average (±*S.E.*) 1265 ± 257 mm above which higher rainfall was associated with a lower incidence (Fig. 4). This same relationship was observed for the mean precipitations and the number of rainy days with a maximum incidence for an average of 164 ± 92 mm monthly rainfall and a low number of rainy days per year (12 ± 10 days per year) (Fig. 4). Higher variance of precipitation drove a decrease in incidence (Fig. 4).

The hottest quarter was the third most important variable with an importance score, *i.e.,* $MSE_{permuted\ variable}/MSE_{model}$ (see Methods Section), of 2.38 (Fig. 3). Although its relationship with leptospirosis greatly differed between provinces (high standard error among ICEs), the partial dependence curve revealed a negative correlation between the incidence and the temperature (Fig. 4). The average temperature of the hottest quarter varied poorly across Thailand but the variance of the range of temperature (reflecting both intra- and inter-monthly temperature variations) highly differed across the area (Supplementary Fig. S2.). We observed a bell-shape relationship between leptospirosis incidence and the variance of T_{range} with the maximum incidence reached for an average (±*S.E.*) of 6.64 ± 3.68 °C.

The variance of topographic slope appeared as the feature of greatest importance (importance score of 2.54) in the SVR (Fig. 3). The incidence linearly decreased with higher slope variance (Fig. 4). The relationship between the mean elevation and the incidence was not linear and the highest

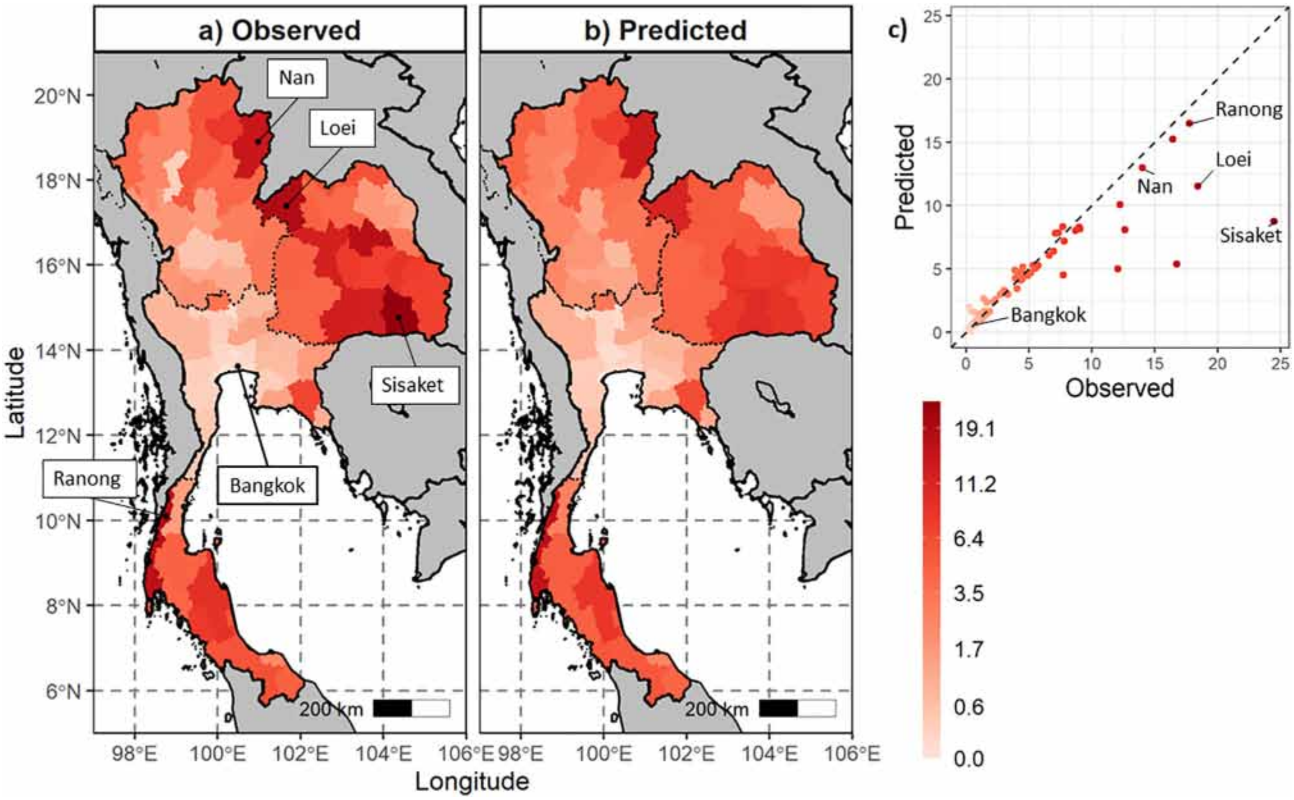


Fig. 2. Observed (a) and predicted (b) incidence of leptospirosis in Thailand from 2003 to 2019 (per 100,000 population). The spatial distribution of the median yearly incidence in Thailand are represented at the provincial scale. The dotted lines show the four regional administrative divisions (North, Northeast, Central and South regions). c) Scatter plot representing the fitted against observed values by province, with the diagonal line showing a hypothetical perfect model.

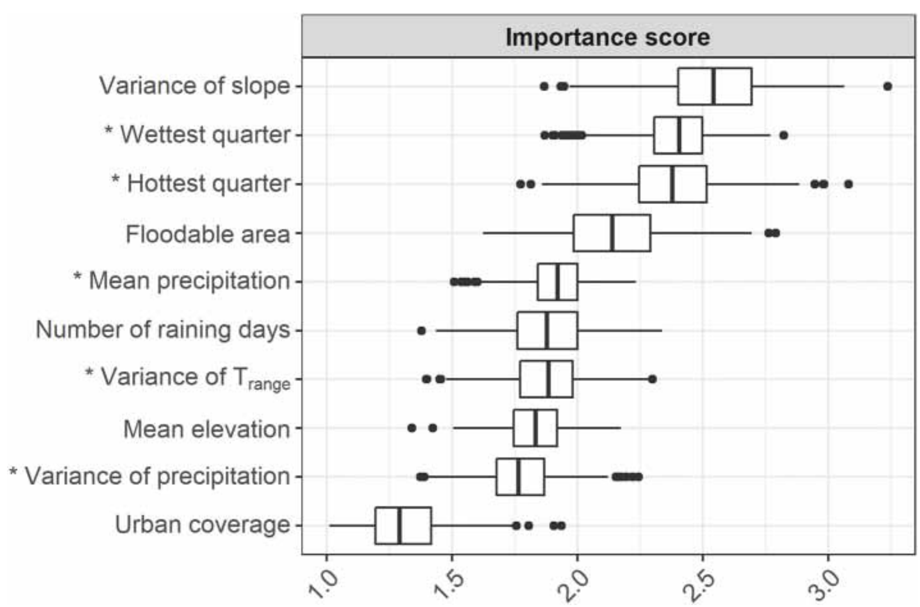


Fig. 3. Importance score of the variables selected in the SVR model. This score compares the increase in MSE caused by repeated permutations (1000 times) of variables values in the dataset (boxplots) to the MSE of the adjusted model (computed as ratio $MSE_{permuted\ variable}/MSE_{model}$). Forecast of 5 climate features computed from CMIP6 climate projections were used to estimate the future evolution of leptospirosis (*).

incidence was obtained for an averaged (± S.E. across provinces) mean elevation of 432 ± 235 m. The percentage of surface covered by floodable area was also an important factor (2.15) and was negatively correlated with the incidence, the lowest incidence corresponding to about 35% of floodable area (Fig. 4 and Supplementary Fig. S4.). Finally, the lowest importance score (1.31) was found for the urban coverage variable. Leptospirosis incidence decreased with wider urbanization, reaching a low plateau at about 30% urban coverage (Figs. 3 and 4).

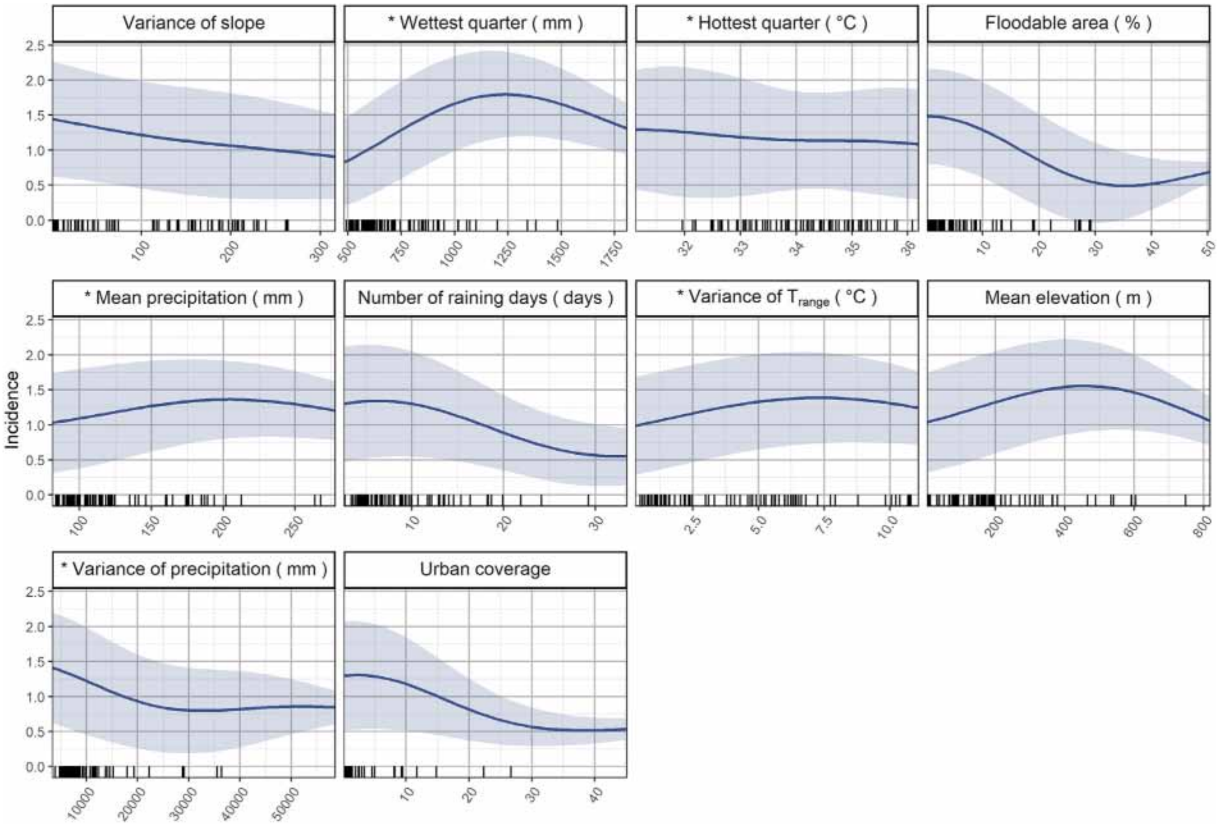


Fig. 4. Partial dependence of leptospirosis to variables modifications. The mean trend of Individual Conditional Expectations (ICEs) curves showing how modelled incidence changes when a single variable changes in a specific province. Standard error on such curves is represented by the shaded ribbon (mean ± sd). The values of the covariates in Thai provinces with which the model is actually constructed are represented along the x-axis with bars. An asterisk (*) indicates the 5 climate variables that will also be computed from CMIP6 climate projections to estimate the future evolution of leptospirosis.

3.3. Revealing the burden of leptospirosis in Southeast Asia

Thailand is a central country in Southeast Asia and shares similar environmental characteristics with Cambodia (Seng et al., 2007), Laos, Vietnam and Myanmar (Supplementary Fig. S6.). Based on the best model built using Thailand surveillance data discussed in the previous section, we estimated the current distribution of leptospirosis in its neighboring countries of mainland Southeast Asia (Fig. 5, 2003–2019 and Fig. 6). About 8% of the provinces had a predicted incidence of leptospirosis above 6.4 cases per 100,000 population. We predicted the highest incidence to be located in the eastern part of the area. In addition to the area defined with high incidence in Thailand, the model identified two additional high incidence spots: 2 provinces in South Cambodia (including Koh Kong) and 3 provinces in East Vietnam (Fig. 5). Two isolated districts of Myanmar, Gangaw and Mongmit, also showed high predicted incidence with estimates of 6.8 and 6.6 respectively. The model predicted very low incidence (below 0.6 yearly cases per 100,000) for 17% of the provinces mostly located in central Thailand (15 provinces), central Cambodia (7 provinces), southern Vietnam (7 provinces) and in the mountainous provinces of Eastern of Myanmar-Northern Laos (7 provinces). At the country scale, Thailand and Laos showed the highest expected incidence, above the overall incidence expected in Southeast Asia (2.34 cases per 100,000 population). However, because of their high population, Thailand and Vietnam represented the highest number of cases accounting for respectively 43% and 34% of cases expected in Southeast Asia (Fig. 6).

3.4. A future decrease in incidence toward a more homogeneous regional distribution

We tested different scenarios of climate change, all resulting in similar trends (Fig. 6 and Supplementary Fig. S7). The best current model among 6 CMIP6 climate projections predicted a global decrease in incidence whatever the scenario considered, with more homogeneous values compared to the heterogeneous incidences predicted under the current climate. The future incidence gradually dropped with more pessimistic climate scenario such that the greatest decrease in incidence was estimated under the SSP5-8.5. For this worst-case scenario of climate change, the variance of incidence across Southeast Asia would drop to 4.59 in the 2041–2060 and then to 0.90 in the 2081–2100 period, *versus* 7.24 in the current period (Figs. 5 and 6). This decrease in human infections would start in the Northwestern part of Southeast Asia during 2041–2060 with Myanmar and Thailand showing a decrease in incidence (Fig. 6). This was particularly observed in Northern Thailand where the incidence in Nan and Loei should drop by 11.8 and 9.7 respectively. This decrease in incidence would progressively encompass the whole area with incidence lower than 4.52 everywhere in the 2081–2100 period compared to a maximum incidence of 24.5 in the current period (Fig. 5). This drift would mainly be driven by the increasing temperatures while the other projected climate variables would show little evolution across periods (Supplementary Figs. S2. and S3.). While most climate models agree on temperature trends, they show more uncertainty on precipitation trends. We purposely kept the measure of such uncertainties by using 6 climate models (Fig. 5, Fig. 6 and Supplementary Fig. S8.).

Despite a global decrease under the SSP5–8.5 scenario, not all regions would evolve similarly in time. We identified 4 temporal profiles of leptospirosis incidence typical of such regional evolutions (Fig. 7). They showed that incidence should decrease for the next 20 years for 90 provinces mostly located in the Northeast of the area (Fig. 7, group 1). Fewer provinces, 61 of the 262 in the area, shared the opposite pattern with a linear increase in incidence mostly located in Southeastern part of the area and in very urbanized areas as Bangkok, Ho Chi Minh City and Hanoi (Fig. 7, group 4). All of these provinces had very low baseline incidence and, despite their

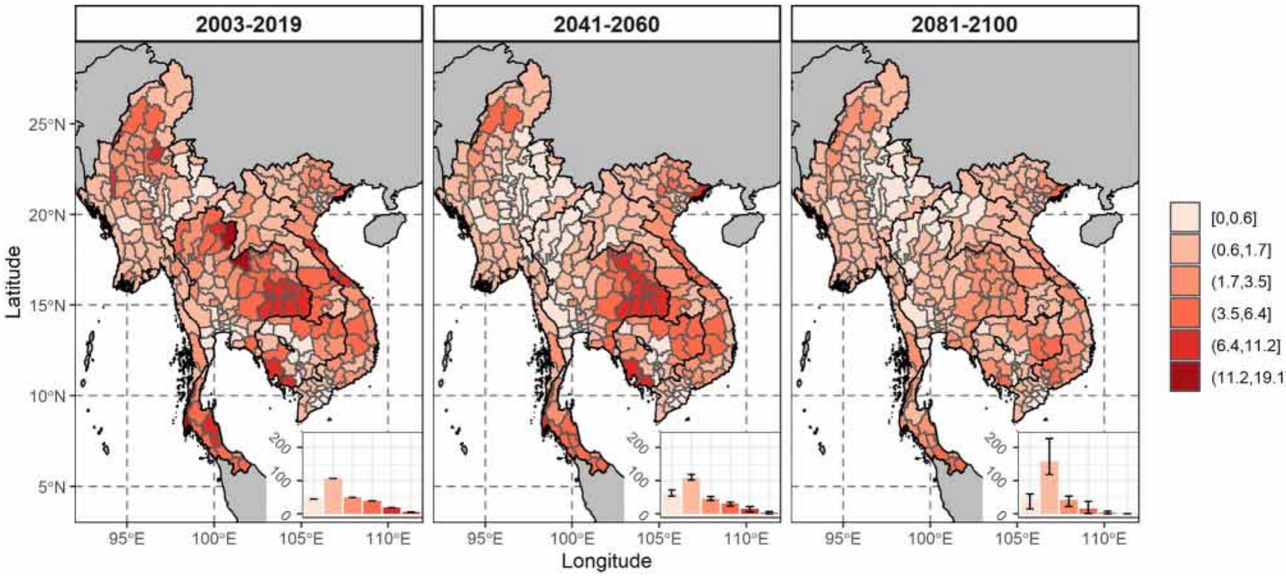


Fig. 5. Distribution of leptospirosis in Southeast Asia and its predicted evolution under the SSP5–8.5 scenario of climate change. Model predictions have been discretized into 6 classes of incidence (given in number of cases per 100,000 population) based on equally spaced intervals of log(*incidence*). Two periods of one of the worst-case climate change scenarios (SSP5–8.5) are represented, the 2041–2060 period (middle panel) and the 2081–2100 period (right panel) for comparison with the current period 2003–2019 (left panel). Histograms give the global distribution of provinces (262 provinces) within each incidence class and error bars describes the 95% interval of the predictions based on the 6 CMIP6 climate models used here (see 2.5 Estimation of leptospirosis distribution and evolution along with climate change).

increasing trend, they would keep low incidence (Fig. 5). In highly populated provinces, low incidence would still lead to a great increase in number of cases that would rise 2 to 4 times the current estimates (corresponding from +24 to +57 cases per year) in the 2081–2100 period compared to now. Finally, the period 2041–2060 appeared as a pivotal period during which the trend of leptospirosis incidence evolution reversed for half of the provinces (Fig. 7, groups 2 and 3). We predicted an increased incidence in 100 provinces (including more than half of Vietnamese and Cambodian provinces) in the period 2041–2060 compared to the current period but only 78 provinces would have such higher incidence in the 2081–2100 period (Fig. 7). The number of cases would reach a peak during this period in Cambodia, Laos and Vietnam whereas it would gradually decrease in Myanmar and Thailand (Fig. 6).

4. Discussion

In this study, we developed the first regional model that describes the spatial distribution of leptospirosis in Southeast Asia using environmental

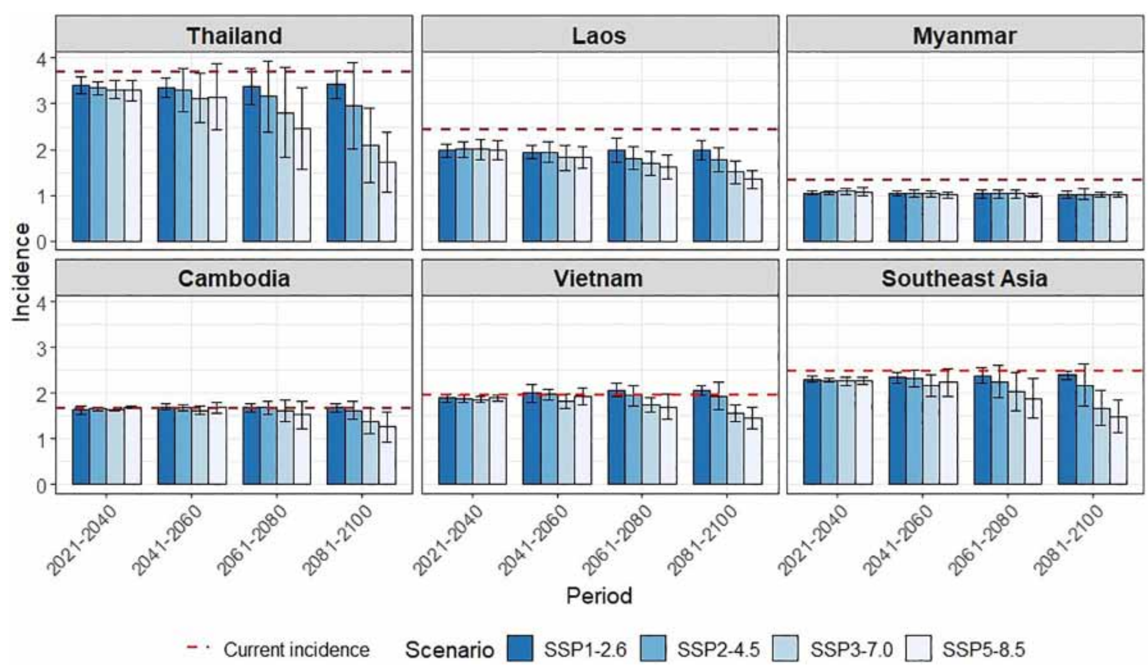


Fig. 6. Future evolution of the leptospirosis incidence aggregated for each country and for mainland Southeast Asia. Incidence was estimated in four 20-years periods from 2021 to 2100 according to 4 scenarios of Shared Socio-economic Pathways (SSP) ranging from the more optimistic to the most pessimistic no climate policy outcomes (SSP1-2.6, SSP2-4.5, SSP3-7.0 and SSP5-8.5). Bar plot and error bars respectively indicate the averaged incidence its associated standard error induced by the 6 climate projection models (MIROC-ES2L, MIROC6, BCC-CSM2-MR, CNRM-CM6-1, CanESM5 and IPSL-CM6A-LR). Current incidence (2003–2019) is indicated with a horizontal line (dashed and red line).

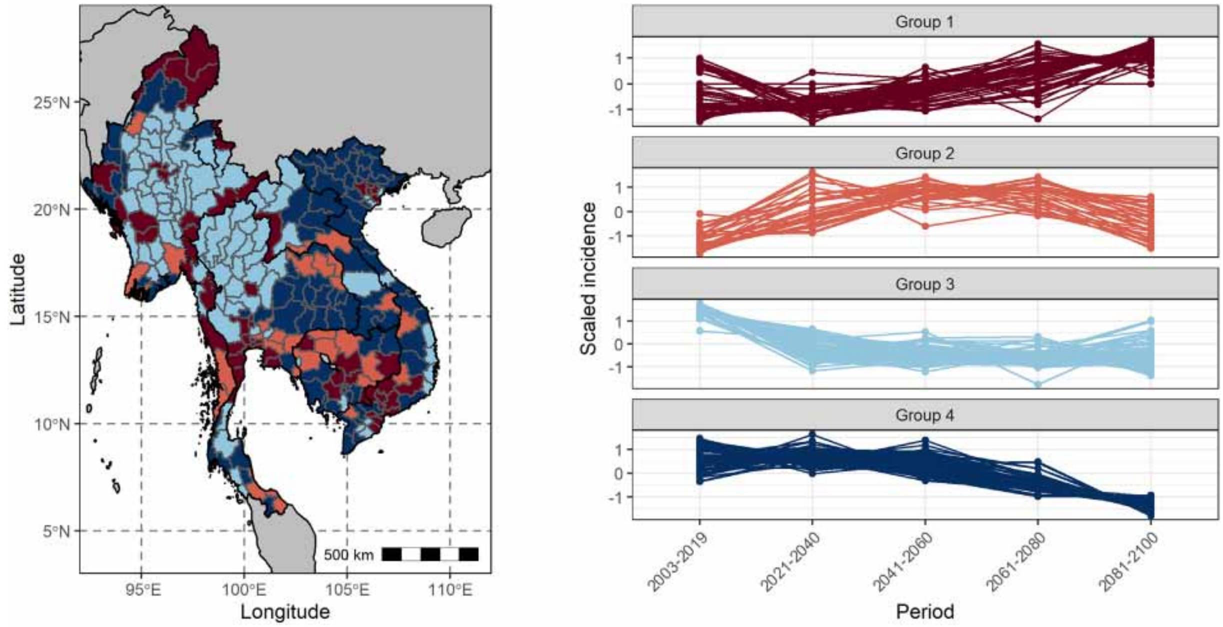


Fig. 7. Predicted temporal dynamics of leptospirosis over time in Southeast Asia under the SSP5-8.5 scenario of climate change from 2003 to 2019 period to 2081–2100. Time evolution patterns of leptospirosis in each province were clustered into 4 groups using K-means. in each province, the incidence was reduced and centered over time prior to clustering. Left panel: spatial distribution of the 4 clusters. Right panel: temporal evolution of the 4 clusters, each line representing one province.

factors. This modelling approach, based on the exploration of a large number of models, allowed 1) identifying the environmental determinants of leptospirosis and 2) revealing the burden of leptospirosis in areas where the disease is not reported (Costa et al., 2015; Victoriano et al., 2009). Given the heterogeneous relationships and interactions between the disease and environmental determinants, we used support vector regression models to study the spatial distribution of leptospirosis (Mohammadinia et al., 2019). Although collinearity does not violate any mathematical assumption for SVR application, we covered the modelling issues raised by a potential collinearity by exploring a large number of variables combinations in our models (Supplementary Fig. S5.) to satisfy the parsimony principle and by estimating variable effects with permutation processes (See Methods 2.4.). Our model achieved great predictive performance that capture the previously described heterogeneous leptospirosis distribution across Thai regions with the high incidence in the Northeastern region (Chadsuthi et al., 2021; MoPH and Bureau of Epidemiology, 2020; Thaipadungpanit, 2007; Wuthiekanun et al., 2007) and the low incidence in the Central region (Hinjoy, 2016; Luenam and Puttanapong, 2019; Narkkul et al., 2021; Suwanpakdee et al., 2015). In addition, the predictions of the model were robust to small changes in the variables both in term of predictive abilities and marginal effect of variables (Supplementary Fig. S9), suggesting that leptospirosis spatial distribution can be robustly explained by environmental and climatic determinants.

The best model retained for leptospirosis estimation strongly relied on climate variable. As expected, rainfall appeared to be a robust determinant of leptospirosis with heavier rainfall associated to higher incidence (Amilasan et al., 2012; Kawaguchi et al., 2008; Tangkanakul et al., 2005; Thaipadungpanit, 2007; Togami et al., 2018; Wuthiekanun et al., 2007). However, we brought into light a threshold after which higher precipitations decreases human infection. Higher variance of precipitation and a great number of rainy days were also associated with fewer leptospirosis. These indicators taken together suggested that excess rainfall in a short period is likely to decrease incidence (Gutiérrez et al., 2019). Although rainfall is able to disperse bacteria and increase human exposure (Lau et al., 2010), excessive rainfall *via* successive events over longer periods could result in flushing and dilution of the environmental reservoir of leptospires (Gutiérrez et al., 2019). The temperature was negatively correlated with the incidence (Chadsuthi et al., 2021) and low variance of the range of temperature was associated with increasing incidence whereas high variance of this same variable was linked to a decreasing in incidence. This may reflect the importance of soil moisture in the persistence of leptospires. Indeed, hot and humid environments have been shown to favor leptospires, while hot and dry climates seem less suitable since desiccation severely impacts their survival (Gutiérrez et al., 2019; Levett, 2001).

Although population density is related to outbreak intensity in suburban settings, landscape variables were considered to be better indicators to understand the spatial distribution of leptospirosis incidence in Southeast Asia where the disease mostly affects agricultural workers (Della Rossa et al., 2016; Dhewantara et al., 2020; Robertson et al., 2012). Two topographic variables were retained in our model for leptospirosis prediction: the mean elevation showing a bell-shaped relationship with incidence and the variance of slope negatively correlated with incidence. These may reflect the fact that mountainous landscapes with greater slope variability favor swift runoffs preventing leptospires from accumulating in the soil and water bodies (Gutiérrez et al., 2019). In contrast, plains and plateaus host farming activities and are more susceptible to contain flood-prone areas in which leptospires could accumulate. Surprisingly, the coverage of urban area was negatively correlated with incidence. Urbanization can increase the risk of flooding (Lau et al., 2010) in peri-urban slums where rodent populations is also high. In contrast, in Asia, leptospirosis most frequently affects rural subsidence farmers (Victoriano et al., 2009). This negative correlation was also observed at the global scale with lower aggregated country-level percent urbanization expected to also reflect poverty (Costa et al., 2015).

Flooding has been described as a trigger for outbreaks (Chadsuthi et al., 2021; Ledien et al., 2017) but when studied at wider spatial and temporal scales, its relationship with leptospirosis is not clearly established (Suwanpakdee et al., 2015). In our model, incidence decreases in provinces with wider flooded area. Leptospirosis is mainly occupational in Thailand and a great part of the agriculture is rice production in paddy fields. The widest floodable areas are concentrated in the irrigated plains of the central region (Supplementary Fig. S1), more developed and industrialized. Intensive farming and mechanization of agriculture can reduce contact of the population with contaminated environment and thus reduce infection (Suwanpakdee et al., 2015; Yanagihara et al., 2007). The agricultural practices of the Northeastern and Southern regions are more traditional, likely increasing the exposure of farmers. These may have been confounding variables of the model. Taken together with the observed protective effect of successive excess of rainfall, highly watered environments may explain why the model shows that these regions are unfavorable for leptospirosis infections. Wider flooded area could also lead to both dilution and flushing of leptospires, reducing the risk of infection (Suwanpakdee et al., 2015).

Our model estimated the highest incidence in Thailand and in Laos countries. This contrasts with a previous study by Costa et al. (Costa et al., 2015), who estimated the highest incidence to be in Vietnam. Although, Thailand is a central country in Southeast Asia and shares similar environmental characteristics with Cambodia (Seng et al., 2007), Laos, Vietnam and Myanmar (Supplementary Fig. S6), the extended study area remains large. There are instances when the variables in countries are outside the range of the Thai settings, on which the model was adjusted (Supplementary Fig. S6). We therefore note that extrapolation of the model to such a wide area goes with a degree of caution, especially when the measured environmental factors are strongly outside of the range covered by our model and when the area of the province (or district) strongly vary (Gracie et al., 2014). Small administrative divisions, mostly urban and peri-urban, distributed all over the area have lower diversity of environments likely to give extreme values of landscape coverage. In addition, some districts of Myanmar, highly watered (coastal districts) or elevated (northern districts) are outside the range of values observed in Thailand where the model was adjusted (Supplementary Fig. S6). Moreover, this model was built based on the national leptospirosis surveillance in Thailand, which includes suspected, probable and confirmed cases. This may lead to under- and over-reporting bias, as leptospirosis has non-specific symptoms common to tropical diseases, which make diagnosis difficult (Goarant, 2016; Victoriano et al., 2009). Such a passive surveillance identifies people seeking medical advice, selecting more severe cases (Goarant, 2016) or population having better access to healthcare, certainly leading to some under-reporting. This bias, hindering the estimation of the true burden of the disease in Thailand, must also have affected our model extension to Southeast Asia. Moreover, our model could not include human behavior, such as walking barefoot, swimming in stream or consuming water from different sources (Narkkul et al., 2021) nor socio-economics aspects, as poverty, low sanitation, rural occupations, agricultural practices and traditional farming (Costa et al., 2015; Narkkul et al., 2021), all known to play a role in the exposure of populations (Mwachui et al., 2015) but not captured by indicators. These patterns can widely differ across and within countries. Neglecting these anthropogenic determinants in the model might explain the underestimation of the incidence in the Northeastern region of Thailand. While extrapolating, the true burden of leptospirosis in Southeast Asia is likely to be underestimated, especially in countries less informed and less developed than Thailand.

The choice of the spatial and temporal scales has been shown to be pivotal in the identification of environmental drivers of leptospirosis (Gracie et al., 2014; Gutiérrez et al., 2019; Suwanpakdee et al., 2015). Our study therefore faces some limitations relative to the aggregation of independent ecological variables over time and at the province or district level that hide the effect of extreme and localized climatic events on human infection. Such extreme events, as flood and heavy rainfall recurrently associated with outbreaks (Amilasan et al., 2012; Kawaguchi et al., 2008; Thaipadungpanit, 2007; Togami et al., 2018), are expected to intensify with climate change (Lau et al., 2010). In this study, we estimated a drift toward lower leptospirosis incidence in Southeast Asia which extent increases with more pessimistic scenario of climate change (see Supplementary Fig. S7.). Considering smaller spatiotemporal pattern such as that described above could bring additional insights (Gutiérrez and Martínez-Vega, 2018; Tabucanon et al., 2021) for the future of leptospirosis in Asia according to climate-policy outcomes.

Our study emphasizes that the quality of climate data for the present-day and future climates are key to understand the fate of Leptospirosis. Presently, global climate model projections such as rainfall projections are recognized to be uncertain in most world regions (Masson-Delmotte et al., 2021). For the future climate, the dataset from worldclim (Fick and Hijmans, 2017) that we used to project Leptospirosis burden, proposes a combination of observed gridded station data superposed to future climate anomalies from an ensemble of climate models. Although we acknowledge that such a method is a crude statistical way to correct for the present-day climate model biases, it does allow to bear some confidence in the projected climates that the direct and uncertain climate outputs cannot provide, especially for rainfall derived variables. Another promising path for climate model uncertainty corrections lies in the use of regional dynamical downscaling from global climate models that should provide more precise and regionally-relevant climate projections. However, the state-of-the art of regional models for the region remains more uncertain than the dataset such as that used in worldclim (Tangang et al., 2019) hence casting doubts about their use for future projections. Improved regional climate downscaling in the future will prompt future improved estimation of local Leptospirosis burden.

Another source of uncertainty arises from the absence of information for some of the forcing variables. For instance, the evolution of urban coverage, number of rainy days and floodable areas were not modified from current values in our projection of leptospirosis. We note that landscape is likely to change in the future with the global trend of urbanization, deforestation and agriculture intensification (Field and Barros, 2014) that could modify the flooding patterns and human exposure (Della Rossa et al., 2016). The fast urbanization process goes with the development of slum settlements where poor sanitation and increased risk of floods gather the conditions for rainfall-associated outbreaks (Costa et al., 2015; Lau et al., 2010). Climate change is expected to exacerbate inequalities especially in Southeast Asia where most inhabitants are involved into environment-dependent occupations (Field and Barros, 2014) making populations more vulnerable to the disease. Oppositely, the industrialization and mechanization of agriculture may reduce the risk of exposure. The combined effects of such climate, landscape and socio-economic changes in the future of leptospirosis remain difficult to assess.

5. Conclusion

Overall, our study focused on the spatial distribution of endemic leptospirosis. Our model achieved good predictive performances while solely focusing on environmental explanatory variables. For the first time, we provided estimates of incidence at provincial and district level and its evolution with climate change using 6 climate models under four scenarios from the most optimistic (temperature increase bounded below 2 °C) to the worst-case no-climate policy outcome. Future work will have to take into account the largest possible number of climate models that were not available in the climate drivers that was used at the time of the study.

CRediT authorship contribution statement

Léa Douchet: Methodology, Investigation, Software, Formal analysis, Visualization, Writing - Original Draft. **Cyrille Goarant:** Investigation, Conceptualization, Writing - Review & Editing. **Morgan Mangeas:** Conceptualization, Methodology, Supervision, Project administration, Writing - Review & Editing. **Christophe Menkes:** Investigation, Conceptualization, Writing - Review & Editing. **Sowapak Hinjoy:** Writing - Review & Editing. **Vincent Herbreteau:** Investigation, Conceptualization, Supervision, Project administration, Writing - Review & Editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the Bureau of Epidemiology of the Ministry of Public Health of Thailand for providing leptospirosis surveillance data. This work was funded by the Agence Française de Développement (AFD), in the

framework of the ECOMORE II project (http://ecomore.org/), coordinated by Institut Pasteur.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.155018.

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