ECOLE DOCTORALE PIERRE LOUIS DE SANTE PUBLIQUE A PARIS
EPIDEMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMEDICALE

Directeur : Pierre-Yves Boëlle
Responsable pour l'Université Paris Cité : Isabelle Boutron

PROPOSITION DE SUJET DE THESE

SIGLE ET NOM DU LABORATOIRE : IPLESP UMRS-1136 INSERM SORBONNE UNIVERSITE
NOM DE L'EQUIPE : MALADIES TRANSMISSIBLES : SURVEILLANCE ET MODELISATION
DIRECTEUR DE THESE : RAPHAELLE METRAS
ADRESSE : 27 RUE DE CHALIGNY, 75012 PARIS, FRANCE

TITRE DE LA THÈSE : SPATIAL RISK ASSESSMENT OF LYME BORRELIOSIS AND TICK-BORNE ENCEPHALITIS: A JOINT MODELLING APPROACH

CO-ENCADRANT EVENTUEL :
EQUIPE DU CO-ENCADRANT :
LABORATOIRE :

PRESENTATION DU SUJET

1. Background

Lyme borreliosis (LB) and tick-borne encephalitis (TBE) are two major tick-borne zoonoses in temperate regions of the world, transmitted in Europe mainly by Ixodes ricinus [1-3]. LB and TBE are caused by the infection with two different pathogens, *Borrelia burgdorferi* sensu lato (Bbsl, spirochete bacteria) and TBE virus (TBEV, a Flavivirus), respectively. In Europe, surveillance has been implemented over the past decades, though heterogeneously. Data so far show that Central Europe is the most affected area where both diseases appear endemic, with LB incidence remaining higher than TBE's [4,5]. In Western Europe, LB is endemic and TBE manifests mainly as foci areas of endemicity or sporadic outbreaks [6,7]. No vaccine is available for LB, and TBE vaccination protocols are applied in few high-risk countries only [8]. The increase in both diseases' incidence and spatial extent [9,10] is a major concern, and needs to be explored more in depth.

Both pathogens' endemicity is allowed by a complex transmission cycle at the interface between Ixodes ticks and several vertebrate species, which can act as reservoir (e.g., rodents and blackbirds) or feeding hosts (e.g., cattle or deer). Humans can get infected through an infectious tick bite. Food-borne transmission is also reported for TBEV [2,3]. Studying the spatio-temporal distribution of LB and TBE incidence therefore requires to account for the circumstances in which humans get exposed, as well as understanding the distribution of infected ticks. Whilst human outdoor activities maybe driven by meteorological factors and/or societal phenomenon, distribution of infected ticks heavily depends on meteorological and environmental factors. The latter, influencing the bio-ecology of the tick vector (questing and feeding activity, and development), also drives the availability of vertebrate hosts (reservoir or feeding) necessary for ticks' blood meal, and therefore the completion of the tick life cycle.

In France, LB and TBE have been reported for several years, displaying a seasonal pattern (May-August), manifesting spatially in similar areas, yet with different intensities. Spatial analysis of LB surveillance data, already conducted by our group in the "One Health" framework, has highlighted the importance of increased vegetation density and mild temperatures in the seasonal incidence of LB in 2016-2021 [11,12]. Whilst this work led to the first LB risk maps, important novel sources of data (examples of novel data are (ii), (iii), (iv) listed in the 'methodology' paragraph) are now available to refine our estimates. In contrast, TBE has never been mapped in our country. Yet, TBE cases have been reported sporadically in the Grand-Est (GE) region since 1968, and since the early 2000s, the number of case reports have increased in frequency and in their spatial extent, affecting the central and Alpine areas (AURA region) [13-15]. In 2020, over 40 cases of meningo-encephalitis were reported in AURA [15], evidencing that the virus has now established beyond GE.

2. Questions

The aim of this PhD is to elucidate the determinants defining *Bbsl* and TBEv spatial distribution in the human populations in France by studying both diseases jointly, in a high-risk region (Grand-Est) and nationally, and to predict high-risk areas for both or either disease, as well as the influence of changing factors (meteorological, environmental, and tick exposure) on disease incidence, as a case study for LB and TBE endemic areas in general.

The specific objectives are:
(1) Review the state-of-the-art mapping methods used for LB and TBE in humans, as well as those methods used to map multiple disease outcomes.
(2) Describe the spatio-temporal pattern of LB and TBE in France since 2009, using descriptive and exploratory space-time statistics by combing the different sources of data available
(3) Identify the common and diverging spatial drivers for LB and TBE and estimate their importance in diseases' distribution at the regional and national levels
(4) Project incidence and maps high-risk areas under different meteorological and environmental scenarios, and generate a series of public health recommendations to control or prevent disease

3. Datasets

The project will use a series of one-of-a-kind datasets, shared by collaborators (see collaborators paragraph), including (i) LB surveillance reports (Reseau Sentinelles), (ii) Antibioclic requests database referring to a patient with Lyme disease; (iii) TBE case reports since 2013 (TBE is notifiable since 2021), (iv) seroprevalence data for both diseases: a nationwide serosurvey from a national Blood donor survey in 2021-2022 (in collaboration with the National Reference Center for arbovirosis and the National Reference Center Borrelia). Further datasets on environmental, meteorological, and animal hosts are also available from open sources (Copernicus, ECDC, ERGO group). Anthropogenic factors aiming at measuring the human exposure to tick-bite will also be used, including crowd-sourcing data (CiTIQUE, Pl@ntNet), and novel prospective data collected by our team (from Grippenet cohort). These will allow mapping the tick/human interface at the national level.

4. Methods

Objective 1:

State-of-the-art. Conduct a literature review on the spatio-temporal modelling methods used to map several outcomes, with a perspective on vector-borne infections.

Objective 2:

2.1. Data collation, management and description. A thorough description of the available datasets will be conducted.

2.2. Identification, sourcing and mapping of space-time risk factors associated with the presence of Lyme and TBE. Key intermediate maps, such as infection in cattle, roe deer, Antibioclic requests, and human exposure to tick bites will also be generated.

Objectives 3 & 4:

Correlations between the spatial distribution of LB and TBE incidence and seroprevalence in humans with underlying parameters (such as exposure to tick bites, environmental variables and land cover, spatial distribution of hosts and their infectious status) will be investigated using exploratory space-time statistics and statistical regression modelling. Examples of such models are multinomial logistic regression or generalized estimating equations for multiple outcomes (LB+/TBE+, LB+/TBE-, LB-/TBE-) [16,17]. Parameter inference will be conducted in a Bayesian framework for spatial and temporal dimensions, using MCMC or Integrated Nested Laplace Approximation [12,18,19]. These models will be used to produce risk maps, and project at-risk areas under different scenarios (such as meteorological or change in the seasonality or spatial extent of human exposure).

5. Papers / deliverables

Paper 1 (Original research): Spatial patterns, intermediate maps, esp. mapping the human exposure to tick-bite, or animal hosts exposure to disease

Paper 2 (Original research): Common and diverging spatial factors for LB and TBE incidence

A repository with the codes generated and the data will also be produced

6. Collaborations

The PhD work proposed is part of a larger project on tick-borne diseases. Therefore, the candidate will interact with several collaborators and data owners (researchers, health officials, associations representatives) within and outside the host laboratory and from different disciplines to ensure that the use of data, the models developed and the recommendations remain realistic and useful in a real-world setting.

We welcome candidates with a background in a quantitative discipline (such as mathematics, physics, biostatistics, ecology, epidemiology) with a keen interest in conducting interdisciplinary research in the field of zoonoses and public health.

7. Timeline

	Semester 1	Semester 2	Semester 3	Semester 4	Semester 5	Semester 6
Objective 1						
Literature review						
Objective 2						
2.1. Data description						
2.2. Risk factors sourcing and mapping						
Paper 1						
Objective 3						
Joint spatial models						
Paper 2						
Thesis writing						

8. References

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PREREQUIS, FORMATION : EPIDEMIOLOGIE ET MODELISATION, STATISTIQUES, PHYSIQUE, MATHEMATIQUES

CONTACT POUR CE SUJET : RAPHAELLE METRAS

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Directeur : Pierre-Yves Boëlle
Responsable pour l'Université Paris Cité : Isabelle Boutron
EMAIL : RAPHAELLE.METRAS@INSERM.FR,
TELEPHONE : +33 (0) 144 738 445

SPECIALITE DE LA THESE

Santé publique - Epidémiologie	☐
Santé publique - Epidémiologie clinique	☐
Santé publique - Epidémiologie sociale	☐
Santé publique - Epidémiologie génétique	☐
Santé publique - Biostatistique	☐
Santé publique - Biomathématiques	☐
Santé publique - Biostatistique et Biomathématiques	☒
Santé publique - Informatique médicale	☐
Santé publique - Imagerie biomédicale	☐
Santé publique - Bioinformatique	☐
Santé publique - Recherches sur les services de santé	☐
Santé publique - Economie de la santé	☐
Santé publique - Science des données	☐
Santé publique – Prévention et promotion de la santé	☐