Spatial epidemiological approaches to inform leptospirosis surveillance and control: a systematic review and critical appraisal of methods

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Summary

Leptospirosis is a global zoonotic disease that the transmission is driven by complex geographical and temporal variation in demographics, animal hosts, and socio-ecological factors. This result in complex challenges for the identification of high-risk areas. Spatiotemporal epidemiological tools could be used to support leptospirosis control programs, but the adequacy of its application has not been evaluated. We searched literature in six databases including Pubmed, Web of Science, EMBASE, Scopus, SciELO, and Zoological Record to systematically review and critically assess the use of spatiotemporal analytical tools for leptospirosis and to provide general framework for its application in future studies. We reviewed 109 articles published between 1930 and October 2018 from 41 different countries. Of these, 65 (56.52%) articles were on human leptospirosis, 39 (33.91%) on animal leptospirosis, and 11 (9.5%) used data from both human and animal leptospirosis. Spatial analytical (n=106) tools were used to to describe the distribution of incidence/prevalence at various geographical scales (96.5%) and to explored spatial patterns to detect clustering and hotspots (33%). A total of 51 studies modeled the relationships of various variables on the risk of human (n=31), animal (n=17) and both human and animal infection (n=3). Among those modeling studies, few studies had generated spatially-structured models and predictive maps of human (n=2/31) and animal leptospirosis (n=1/17). In addition, nine studies applied time-series analytical tools to predict leptospirosis incidence. Spatiotemporal analytical tools have been greatly utilized to improve our understanding on leptospirosis epidemiology. Yet the quality of the epidemiological data, the selection of covariates and spatial analytical techniques should be carefully considered in future studies to improve usefulness of evidence as tools to support leptospirosis control. A general framework for the application of spatial analytical tools for leptospirosis was proposed.

Keywords: Leptospirosis, eco-epidemiology, environmental epidemiology, GIS, modeling, geostatistics, mapping, One Health

Impacts

- The increase trend in the utilization of spatial epidemiological approaches in the field of human and animal leptospirosis demonstrating the importance of such framework to provide better knowledge on disease aetiology and prediction models.
- The value of evidence is greatly depends on the quality of the epidemiological data and the selection of risk factors and spatial analytical techniques.
- General framework on the use of spatial analytical tools are developed to provide guidance for future works and to improve the the usefulness of such tools to support leptospirosis control.

1. Introduction

Leptospirosis is a zoonotic disease of major public health and animal health importance caused by pathogenic spirochete belonging to the genus *Leptospira* that is common in tropical and sub-tropical countries (Bharti et al., 2003; Faine, Adler, Bolin, & Perolat, 1999). Annualy worldwide, it is estimated that at least one million human cases and 58,900 deaths occur leading to the lost of approximately 2.9 million disability-adjusted life-years (DALYs) (Costa et al., 2015; Torgerson et al., 2015). In animals, *Leptospira* infection can lead to reproductive failure in livestock (e.g., abortion, premature progeny, stillbirths, infertility, and fetal mummification), decreased milk production and systemic illness, which may be fatal and cause significant economic losses (Donahue, Smith, Poonacha, Donahoe, & Rigsby, 1995; Ellis, 2015; Martins et al., 2012). Hence, it is imperative to improve the delivery of disease control strategies in both human and animals.

Leptospirosis transmission is driven by a complex interaction of environmental, socioeconomic, demographic and individual determinants which result in considerable geographical and temporal variation in infection risk (C. L. Lau, Smythe, Craig, & Weinstein, 2010; Mwachui, Crump, Hartskeerl, Zinsstag, & Hattendorf, 2015). Infection may occur through contact with infected reservoir animals urine and tissues, or with *Leptospira*-contaminated soil or water. More than 300 serovars of *Leptospira* spp, categorized into 25 serogroups, have now been identified worldwide (Levett, 2001). There are 10 pathogenic species and five intermediate species which occasionally cause mild clinical manifestations (Xu et al., 2016). A wide range of animals including domestic (e.g., livestock and companion animals), wildlife, and rodents have been identified as *Leptospira* carriers (Adler & de la Pena Moctezuma, 2010; Haake & Levett, 2015).

The incidence of leptospirosis is geographically and temporally varied and it is strongly associated with climatic, environmental and local socioeconomic factors (Cosson et al., 2014). Higher incidence is reported in tropical, humid and temperate regions, especially during the wet season, disproportionately affects deprived populations both in rural and urban areas (Albert I. Ko, Reis, Dourado, Johnson, & Riley, 1999). Numerous leptospirosis outbreaks, particularly in urban setting are often linked with severe flooding resulting from heavy rainfall or cyclones (Amilasan et al., 2012; Dechet et al., 2012; Albert I. Ko et al., 1999). In rural areas, leptospirosis is closely correlate with agricultural processes such as rice paddy harvesting and livestock husbandry (Ellis, 2015; Prabhakaran, Shanmughapriya, Dhanapaul, James, & Natarajaseenivasan, 2014). Ecological degradation of living conditions due to rapid population growth and urbanization coupled with climate change are considered to be some of the most important driving forces behind current and future leptospirosis outbreaks (C. L. Lau et al., 2010)

The complexity in transmission pathways for leptospirosis constitute a major challenge for control strategies, especially in remote and poor resource endemic areas. There is a need to develop accurate and cost-effective tools to improve existing surveillance and strengthen control strategies. Geographic information systems (GIS), remote sensing (RS), and geospatial statistics tools have now been greatly enhanced and used in public health studies and have the potential to improve disease epidemiology and control. In order to gain more values from such tools, the present paper is aimed to comprehensively review the use of spatial analytical methods in leptospirosis studies to help improve research designs and lay foundation for further leptospirosis studies to support more effective surveillance and control programs. As leptospirosis transmission strongly involves interdependent interaction between animals, human and environment (Rabinowitz et al., 2013), in this paper we focused on how spatial and temporal

approaches have been used in leptospirosis studies of both animals and humans. Future research directions on the application of spatiotemporal analysis in leptospirosis are also discussed.

2. Materials and methods

2.1 Search strategy

Using standard systematic review and meta-analysis (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & The Prisma Group, 2009), we searched Pubmed, Web of Science, EMBASE, Scopus, SciELO, and Zoological Record for peer-reviewed articles published until October 31st, 2018. In order to identify other relevant articles not captured by our initial searches, we manually searched the reference lists of included articles (Hopewell, Clarke, Lefebvre, & Scherer, 2007). To retrieve relevant articles, we used a combination of the following search terms: "spatial", "spatiotemporal", "geographical information system", "mapping", "remote sensing", "prediction", "outbreak", "cluster" and "leptospirosis" (Supporting information: Table S1). No restrictions on language or publication date were applied.

All articles retrieved from the databases were stored and checked for duplicates using EndNote™ (Thomson Reuters, Philadelphia, PA, USA) reference manager. All unique titles and abstracts (when available) were screened to identify relevant publications that met inclusion criteria by one reviewer (PWD). Full review was then applied to all articles available in full-text for eligibility by two authors (PWD and RJSM). Eligible articles were grouped into three categories: studies that used data on (i) human, (ii) animal, or (iii) both human and animal infection.

2.2 Inclusion and exclusion criteria

Studies were eligible for inclusion if they applied one or more spatial analyses techniques

including visualization (defined as mapping leptospirosis infection data to illustrate spatial patterns of disease distribution), exploration (defined as applying statitistical tools to analyse such patterns, including whether the infection data were clustered or random), and modelling (e.g., utilize spatial and non-spatial data to explore associated risk factors for infection, to quantify spatial variation in risk, and to develop spatial and/or temporal predictive models).

Papers were excluded if: (i) abstract or full paper not available; (ii) experimental design studies, case series or case reports, studies on the genetic characterization of *Leptospira* spp. without involving spatial analyses; (iii) ecological or environmental surveys associated with animal reservoirs without providing *Leptospira* infection data; (iv) non-spatial studies; (v) studies that dealt with seasonality with no further attempt to develop temporal predictive models; or (vi) short communications, conference proceedings, commentaries, review articles, books or book sections.

2.3 Data extraction

For each eligible article, we extracted and summarized data on study location, year of publication, study design (e.g., cross-sectional, case-control, cohort), leptospirosis epidemiological data (e.g., human, animal, or both) and diagnostic methods used, study objective (e.g., disease mapping, detect clustering, spatial and/or temporal modeling), spatial and/or temporal analysis methods (e.g., visualisation, exploration, modelling), predictors (e.g. environmental, climatic, socioeconomic, demographic), and outcomes (e.g. maps, findings).

3. Results

3.1 General characteristics of studies included in the review

A total of 1468 records were identified from six databases and 23 additional records were identified through manual searches from bibliographic lists of included papers. A total of 690 unique records remained after the removal of 778 duplicates. A total of 263 papers published until October 2018 met our inclusion criteria were included for full-text review. After full-text review, a total of 115 articles from 41 countries were finally included in our systematic review (Figure 1). The trend in number of publications reporting the use of spatiotemporal approaches to understand the epidemiology of human and/or animal leptospirosis has been increasing with most studies occurring after 2010 (Figure 2). A total of 65 studies used data on human infection, 39 studies used animal infection data, and 11 studies used data on both human and animal infection. Studies were performed either at the sub-national (n=79/115) level, national level (n=35/115) or regional level (n=1/115). No global or continental-scale studies were reported in any of the papers included in our review.

The majority of leptospirosis studies were reported from the Americas, especially in Brazil (24.61%, n=16/65) for human leptospirosis studies and the USA (28.20%, n=11/39) for animal leptospirosis studies (Figure 3). Studies using both human and animal infection data were conducted in eight countries, mainly in Southeast Asia (45%, n =5/11), including Thailand, Indonesia, and the Philippines.

From the total of 115 eligible articles, 106 (92.17%) studies in 37 countries dealt with spatial analyses which included visualization (90.56%, n=97/106), exploration (33.01%, n=35/106), and modeling (47.16%, n=50/106). Whereas, nine articles applied temporal or time-series modeling

techniques as tools to predict human (n=7) and animal (n=2) leptospirosis incidence. Among those studies that included spatial analysis, few studies (15.09% , n=16/106) conducted visualisation, exploration, and modeling concurrently (Della Rossa et al., 2016; Gracie, Barcellos, Magalhaes, Souza-Santos, & Barrocas, 2014; C. L. Lau, Clements, et al., 2012; Helen J. Mayfield et al., 2018; Miyama et al., 2018; Mohd Radi et al., 2018; R. K. Raghavan, Brenner, Higgins, Shawn Hutchinson, & Harkin, 2012; Robertson, Nelson, & Stephen, 2012; Soares, Latorre Mdo, Laporta, & Buzzar, 2010; Suwanpakdee et al., 2015; Tassinari et al., 2008) (**Supporting information: Table S2**).

3.2 Leptospirosis infection data sources, case definitions and diagnostic tests

Leptospirosis infection data were mostly obtained from national notification system (45.21%, n=52/115), medical records or laboratory databases (include hospital admission database) (22.60%, n=26/115). Only 40 studies (34.78%, n=40/115) used infection data generated by surveys. Most studies were cross-sectional (86.95%, n=100/115), few (6.08%, n=7/115) were case-control studies (Ghneim et al., 2007; Hennebelle, Sykes, Carpenter, & Foley, 2013; R. Raghavan, Brenner, Higgins, Van der Merwe, & Harkin, 2011; R. K. Raghavan, Brenner, Harrington, Higgins, & Harkin, 2013; Suryani, Pramoedyo, Sudarto, & Andarini, 2016; Ward, 2002a; Ward, Guptill, & Wu, 2004) and only six studies (5.21%) employed a prospective cohort design (Deshmukh et al., 2018; Hagan et al., 2016; A. I. Ko, Galvão Reis, Ribeiro Dourado, Johnson Jr, & Riley, 1999; Ledien et al., 2017; Mišić-Majerus, 2014; Reis et al., 2008).

In terms of diagnostic approaches, human infection data used were most commonly based on microscopic agglutination test (MAT) (50.76%, n=33/65), enzyme linked immunosorbent assay (ELISA) (33.84%, n=22/65) or polymerase chain reaction (PCR) (13.84%, n=9/65). Eleven studies used culture in combination with serological tests or PCR (Biscornet et al., 2017; Desvars

et al., 2011; Jansen et al., 2005; Pijnacker et al., 2016; Rood, Goris, Pijnacker, Bakker, & Hartskeerl, 2017; Slack, Symonds, Dohnt, Corney, & Smythe, 2007; Slack, Symonds, Dohnt, & Smythe, 2006; Soares et al., 2010; Suwanpakdee et al., 2015; Tassinari et al., 2008; Weinberger, Baroux, Grangeon, Ko, & Goarant, 2014) to diagnose human infection. As with human studies, the majority of animal studies also used MAT (53.84%, n=21/39) to determine animal infection status, and three studies used ELISA only (Miyama et al., 2018; Pijnacker et al., 2016; Soares et al., 2010). Eight studies used culture in combination with serological tests or PCR.

Thirty-one (47.69%, n=31/65) human leptospirosis studies, four studies (10.25%, n=4/39) on animal leptospirosis, and four studies (36.36%, n=4/11) that used animal and human infection data did not clearly describe the case definitions of leptospirosis infection. And, 28 studies did not specifically describe the diagnostic techniques used.

3.3 Mapping the geographical distribution of leptospirosis

3.3.1 Mapping human leptospirosis data

Most spatial studies (96.55%, n=56/58) produced human infection maps and most utilized data obtained from the national disease surveillance notification systems (73.21%, n=41/56). Maps were produced to depict incidence or prevalence in certain administrative areas (48.21%; n=27/56) either at regional (n=1) (M. Schneider et al., 2017), national (n=11) (Gonwong et al., 2017; Jansen et al., 2005; C. L. Lau, Clements, et al., 2012; Massenet, Yvon, Couteaux, & Goarant, 2015; Robertson et al., 2012; Rood et al., 2017; M. C. Schneider et al., 2012; Shi, Tu, & Li, 1995; Stevens, Carter, Kiep, Stevenson, & Schneeweiss, 2011; van Alphen et al., 2015; Zhao et al., 2016) or sub-national scales (n=15) (Barcellos, Lammerhirt, de Almeida, & dos Santos, 2003; Barcellos & Sabroza, 2000; Chaiblich, Lima, Oliveira, Monken, & Penna, 2017; Garcia-Ramirez et al., 2015; Gracie et al., 2014; Herbreteau et al., 2006; A. I. Ko et al., 1999; C. L. Lau,

Skelly, Dohnt, & Smythe, 2015; Mišić-Majerus, 2014; Mohammadinia, Alimohammadi, & Saeidian, 2017; Mohd Radi et al., 2018; Myint et al., 2007; M. C. Schneider et al., 2015; Soares et al., 2010; Vega-Corredor & Opadeyi, 2014). Twelve studies used Kernel density estimation technique to generate smoothed distribution maps of disease counts, risk or population density (Chaiblich et al., 2017; Cook et al., 2017; de Melo et al., 2011; Deshmukh et al., 2018; Filho et al., 2014; C. L. Lau, Dobson, et al., 2012; C. L. Lau, Skelly, Smythe, Craig, & Weinstein, 2012; Mohd Radi et al., 2018; Reis et al., 2008; Rood et al., 2017; Tassinari Wde, Pellegrini Dda, Sabroza, & Carvalho, 2004; Vega-Corredor & Opadeyi, 2014). Two studies constructed suitability maps for leptospirosis occurrence at national-level (Sanchez-Montes, Espinosa-Martinez, Rios-Munoz, Berzunza-Cruz, & Becker, 2015; Zhao et al., 2016).

Seroprevalence maps were produced by three studies (5.35%, n=3/56) based on ELISA (Gonwong et al., 2017) or MAT (C. L. Lau, Clements, et al., 2012; C. L. Lau et al., 2016). Seropositivity maps were created based on serological (MAT) data collected from the field surveys (C. L. Lau, Dobson, et al., 2012; C. L. Lau, Skelly, et al., 2012). Six studies mapped the distribution of predominant serovars identified from field studies (C. L. Lau, Clements, et al., 2012; C. L. Lau, Dobson, et al., 2012; C. L. Lau et al., 2015; C. L. Lau, Skelly, et al., 2012; Myint et al., 2007; Slack et al., 2007). No serogroup or serovar distribution maps at regional and global scale were reported. Spatiotemporal maps were created (21.42%, n=12/56) (Baquero & Machado, 2018; Dhewantara et al., 2018; Garcia-Ramirez et al., 2015; Gracie et al., 2014; Hagan et al., 2016; C. L. Lau et al., 2015; Robertson et al., 2012; Soares et al., 2010; Sulistyawati, Nirmalawati, & Mardenta, 2016; Suwanpakdee et al., 2015; Tassinari Wde et al., 2004; Tassinari et al., 2008; van Alphen et al., 2015) to illustrate changes in distribution (Della Rossa et al., 2016; Gracie et al., 2014; C. L. Lau et al., 2015; M. C. Schneider et al., 2012; Soares et al., 2010;

Sulistyawati et al., 2016; Suwanpakdee et al., 2015; Tassinari Wde et al., 2004; Tassinari et al., 2008), disease rates/risks (Baquero & Machado, 2018; Garcia-Ramirez et al., 2015; Hagan et al., 2016; Robertson et al., 2012; Suwanpakdee et al., 2015; van Alphen et al., 2015) or burden in terms of disability-adjusted life years (DALYs) (Dhewantara et al., 2018). One set of sub-national spatiotemporal maps describing changes in serovar-specific cases was produced at state-level in Australia (C. L. Lau et al., 2015). Summary of the studies on mapping leptospirosis is provided Supporting information: Table S3-S4.

3.3.2 Mapping animal leptospirosis data

Thirty-four studies used mapping approaches to describe spatial heterogeneity in incidence/prevalence, serostatus, or distribution of *Leptospira* infections among various reservoir animals including companion animals, livestock, rodents, and wildlife. Few studies created prevalence maps at national (2.94%; n=1/34) (Suwancharoen et al., 2016) or sub-national (14.70%; n=5/34) (Filho et al., 2014; Hesterberg et al., 2009; Machado et al., 2016; Scolamacchia et al., 2010; Silva et al., 2018) levels. The infection data of companion animals (e.g. dogs) were obtained commonly from laboratory databases/medical records deposited at veterinary clinics (32.35%, n=11/34). Serovar-specific prevalence in livestock was mapped (8.82%, n=3/34) in Australia (J. K. Elder, McKeon, Duncalfe, Ward, & Leutton, 1986; Jean K. Elder & Ward, 1978) and Japan (Miyama et al., 2018). Livestock, rodents or wildlife animals infection data were often collected from animal sampling. Few studies reported the use of Kernel density risk maps (n=2) (Filho et al., 2014; Hashimoto et al., 2015) and suitability maps (n=1) (Dobigny et al., 2015). No spatiotemporal maps for animal leptospirosis was reported.

3.3.3 Mapping human and animal infection data

Eleven articles used both human and animal infection data (Assenga, Matemba, Muller, Mhamphi, & Kazwala, 2015; Biscornet et al., 2017; S. Chadsuthi et al., 2017; Cipullo & Dias, 2012; Della Rossa et al., 2016; Fonzar & Langoni, 2012; Hurd, Berke, Poljak, & Runge, 2017; Pijnacker et al., 2016; Sumanta, Wibawa, Hadisusanto, Nuryati, & Kusnanto, 2015; Villanueva et al., 2014; Widiastuti, Sholichah, Agustiningsih, & Wijayanti, 2016), but only 64% (n=7/11) of studies incorporated both human and animals infection data into their maps. One study created a national-level seroprevalence map for both human and animals (S. Chadsuthi et al., 2017). At the sub-national level, six studies mapped the geographic co-distribution of serogroups (Assenga et al., 2015; Villanueva et al., 2014) or *Leptospira* seropositivity (Cipullo & Dias, 2012; Fonzar & Langoni, 2012; Sumanta et al., 2015; Widiastuti et al., 2016) in both human and animals. No maps have been produced on describing spatial temporal changes in risks were identified in this group of study.

3.4 Exploratory analysis: detecting spatial autocorrelation and disease clustering

3.4.1 On studies that used human infection data

A wide range of classic global and local spatial clustering analyses were used to investigate large-scale and small-scale variations in patterns of disease distribution (Table 1; Supporting information: Table S5). Eight studies used global Moran's *I* to test spatial clustering on areal data (Cook et al., 2017; Della Rossa et al., 2016; Goncalves et al., 2016; Gracie et al., 2014; Mohammadinia et al., 2017; Rood et al., 2017; Soares et al., 2010; Suryani et al., 2016). Two studies analysed clustering of point data by using global Moran and average nearest neighbor methods (Mohd Radi et al., 2018; Suryani et al., 2016). While Knox test was used to assess global spatial clustering of the leptospirosis over space and time (Bennett & Everard, 1991). Localized spatial clustering techniques were applied to determine hotspots, including Local Indicators of Spatial Association (LISA) (n=3) (Mohd Radi et al., 2018; Rood et al., 2017; Soares et al., 2010) and Getis and Ord's (G_i^*) (n=3) (Hassan & Tahar, 2016; Helen J. Mayfield et al., 2018; Suwanpakdee et al., 2015). Both global and local tests for clustering were only applied in few number of studies (14.28%) (n=3/21) (C. L. Lau, Clements, et al., 2012; Rood et al., 2017; Soares et al., 2010).

Locating the high-risk clusters across space, seven studies used SaTScan (M. Kulldorff & N. Nagarwalla, 1995) at national (Gutierrez & Martinez-Vega, 2018; C. L. Lau, Clements, et al., 2012; Massenet et al., 2015; Robertson et al., 2012) and sub-national scale (Deshmukh et al., 2018; Sulistyawati et al., 2016; Tassinari et al., 2008). The maximum circular spatial window was often set at 50% (Gutierrez & Martinez-Vega, 2018; C. L. Lau, Clements, et al., 2012; Massenet et al., 2015; Sumanta et al., 2015) of the population at risk. The temporal window used ranged from 30 days (Tassinari et al., 2008) to one year (Massenet et al., 2015) although

five studies did not explicitly define spatial or temporal windows (Deshmukh et al., 2018; Robertson et al., 2012; Sulistyawati et al., 2016).

3.4.2 On studies that used animal infection data

Eleven articles tested for global or local spatial clustering on the animal infection data. Few studies applied both global and local tests (n=2) (Alton, Berke, Reid-Smith, Ojkic, & Prescott, 2009; Hennebelle et al., 2013). A variety of methods were used including global Moran's *I* (n=1) (Alton et al., 2009), Cuzick and Edwards' *k*-nearest neighbor and variogram (n=3) (Hennebelle et al., 2013; R. K. Raghavan et al., 2012; Scolamacchia et al., 2010) to detect spatial clustering of infected animals. Nine studies investigated clusters of infected animals using scan statistics including spatial scan test, temporal and spatial scan statistics, spatial permutation test (69.23%, n=9/13) (Alton et al., 2009; da Silva et al., 2006; Gautam, Guptill, Wu, Potter, & Moore, 2010; Hennebelle et al., 2013; Himsworth et al., 2013; Miyama et al., 2018; Nicolino, Lopes, Rodrigues, Teixeira, & Haddad, 2014; Sumanta et al., 2015; Ward, 2002a).

3.4.3 On studies that used both human and animal infection data

Only one study explored spatial pattern of both human and animal infection data. This study used a variety of spatial clustering methods including Moran's *I* and Geary's c as well as employing several different cluster detection techniques using SaTScan and FlexScan software (Hurd et al., 2017).

3.5 Modeling risk of leptospirosis infection and spatial risk prediction

3.5.1 Modeling risk of human infection

Thirty-one studies (53.44%, n=31/58) quantified the effect of a set of selected explanatory variables on leptospirosis incidence/prevalence, at national-level (n=15/31) and sub-national

level (n=17/31) (Table 2). The summary of studies on modelling leptospirosis risk was detailed in Table S6. Most studies assessed the association between environment (e.g., land use, altitude, flood risk) (n=29/31) or climatic factors (e.g., precipitation) (n=18/31) and leptospirosis incidence/prevalence (Figure 4). Half of the studies utilized environmental data, including land cover, elevation, Normalized Difference Vegetation Index (NDVI) Normalized Difference Water Index (NDWI) and climatic data obtained from remote-sense databases (e.g. MODIS, Landsat) (Baquero & Machado, 2018; Gracie et al., 2014; C. L. Lau, Clements, et al., 2012; C. L. Lau, Dobson, et al., 2012; C. L. Lau et al., 2016; M. C. Schneider et al., 2012; Suwanpakdee et al., 2015; Vega-Corredor & Opadeyi, 2014; Zhao et al., 2016) (Supporting Table S7). A recent study proposed the use of Modified NDWI to estimate the risk of *Leptospira* infection following flood (Ledien et al., 2017).

About half of modeling studies included host-related variables such as the presence of animals (e.g., rodents, pigs, dogs, livestock) or animal population size or density into the models (Cook et al., 2017; Dozsa, Monego, & Kummer, 2016; Hagan et al., 2016; C. L. Lau, Clements, et al., 2012; C. L. Lau, Dobson, et al., 2012; C. L. Lau et al., 2016; Helen J. Mayfield et al., 2018a; H. J. Mayfield et al., 2018b; Reis et al., 2008; M. C. Schneider et al., 2012; Suwanpakdee et al., 2015; Zhao et al., 2016). Animal hosts data were collected either from animal surveys (e.g., trapping), livestock census data, or from publicly available GIS databases (e.g., Food and Agricultural Organization, FAO- GeoNetwork).

Twenty-one studies (67.72%, n=21/31) included socioeconomic variables (e.g., population density, income, agricultural production and urbanization) into their models. Population density (Ledien et al., 2017; H. J. Mayfield et al., 2018; Zhao et al., 2016) and socioeconomic indicators (e.g., GDP or poverty rate) (Baquero & Machado, 2018; Helen J. Mayfield et al., 2018a; H. J. Mayfield et al., 2018b; M. C. Schneider et al., 2015; Zhao et al., 2016) were the most common predictors included in the models. Individual-level variables (e.g., age, gender,

occupation, education/literacy, behavioral risk, or ethnicity) were incorporated in 16 out of 31 (51.61%) studies.

Traditional regression analyses were the most common statistical modelling technique used to quantify the association between these variables and leptospirosis incidence/prevalence (Table 2). Simultaneous autoregressive models (n=1) (Rood et al., 2017) and boosted regression tree (BRT) models (n=1) (Ledien et al., 2017) were also reported. To address the spatial non-stationarity of relationships between the spatial distribution of leptospirosis incidence and environmental and sociodemographic factors, five studies applied geographically weighted regression (GWR) (Helen J. Mayfield et al., 2018a; Mohammadinia et al., 2017; Mohd Radi et al., 2018; Vega-Corredor & Opadeyi, 2014; Widayani, Gunawan, Danoedoro, & Mardihusodo, 2016). Two studies used ecological niche modelling using Maxent (Zhao et al., 2016) and Genetic Algorithm for Rule-set Production (GARP) (Sanchez-Montes et al., 2015) at a national scale (Sanchez-Montes et al., 2015; Zhao et al., 2016), and three studies applied a Bayesian approach to their analyses (n=3) (Baquero & Machado, 2018; Hagan et al., 2016; Reis et al., 2008). In addition, the spatially-explicit Bayesian Networks (BNs) have been introduced by one Fijian study (H. J. Mayfield et al., 2018b).

Overall, only two studies completely constructed spatially-structured models (n=2/31) (C. L. Lau, Clements, et al., 2012; Rood et al., 2017) in which model parameters were estimated (SAR and logistic regression, respectively), global and local spatial autocorrelation in the residuals of the models were tested (using global Moran's *I* and semi-variogram), and spatial predictive maps were generated.

3.5.2 Modelling risk of animal infection

Seventeen studies (43.36%, n=17/39) conducted in six countries assessed the association between incidence (n=7) (Ghneim et al., 2007; Major, Schweighauser, & Francey, 2014; R. Raghavan et al., 2011; R. K. Raghavan et al., 2013; R. K. Raghavan et al., 2012; Ward et al., 2004; White et al., 2017) or prevalence (n=10) (Alton et al., 2009; Bier et al., 2012; Bier et al., 2013; Biscornet et al., 2017; J. K. Elder et al., 1986; Jean K. Elder & Ward, 1978; Himsworth et al., 2013; Ivanova et al., 2012; Miyama et al., 2018; Silva et al., 2018) with various predictors at national (n=6) and sub-national (n=11) levels. As with human studies, the effect of physical environmental (64.70%, n=11/17) (Alton et al., 2009; Biscornet et al., 2017; J. K. Elder et al., 1986; Ghneim et al., 2007; Ivanova et al., 2012; R. Raghavan et al., 2011; R. K. Raghavan et al., 2013; R. K. Raghavan et al., 2012; Silva et al., 2018; Ward et al., 2004; White et al., 2017) and climatic factors (52.94%, n=9/17) (J. K. Elder et al., 1986; Jean K. Elder & Ward, 1978; Ghneim et al., 2007; Himsworth et al., 2013; Ivanova et al., 2012; Major et al., 2014; Silva et al., 2018; Ward et al., 2004; White et al., 2017) on animal infections were the most commonly studied. Nine studies used RS-based environmental data (Dobigny et al., 2015; Ghneim et al., 2007; Ivanova et al., 2012; R. Raghavan et al., 2011; R. K. Raghavan et al., 2013; Silva et al., 2018; Ward et al., 2004; White et al., 2017) including land cover/land use, elevation, or slope (Supporting information: Table S7). Eight studies included parameters on the presence of other animal species in their models (Bier et al., 2012; Bier et al., 2013; Ghneim et al., 2007; Miyama et al., 2018; R. K. Raghavan et al., 2012; Silva et al., 2018; Ward et al., 2004; White et al., 2017). Only three studies assessed the role of socioeconomic covariates (e.g., household income of the owner) on animal infection (n=2) (R. K. Raghavan et al., 2012; Silva et al., 2018; White et al., 2017). The individual-level variables, such as animal age, sex, breed, and behaviors, were less reported (n=4) (Alton et al., 2009; Bier et al., 2013; Himsworth et al., 2013; Silva et al., 2018).

In terms of modeling techniques, regression models were most commonly used (n=12/17) (Table 2). Among those, only three studies accounted for spatial autocorrelation in the residual of the models (R. Raghavan et al., 2011; R. K. Raghavan et al., 2013; R. K. Raghavan et al., 2012). Using boosted regression tree, one study generated a national-scale predictive map of canine leptospirosis in the USA (White et al., 2017), but this study did not address spatial autocorrelation in the residuals or prediction uncertainty. None of studies generated spatially-structured prediction maps for animal leptospirosis incidence/prevalence.

3.5.3 Modeling risk of both human and animal infection

Three articles from three countries assessed the effect of various covariates on both animal and human infection (n=3/11) (S. Chadsuthi et al., 2017; Della Rossa et al., 2016; Hurd et al., 2017). All of the them focused on the role of environmental factors and climate on human and animal infection. Of these, only two studies generated spatially-structured models and addressed spatial autocorrelation (Della Rossa et al., 2016; Hurd et al., 2017). No reviewed studies generated spatial prediction maps for both human and animal incidence/prevalence.

3.6 Temporal modeling as tools for leptospirosis outbreak detection

Nine studies performed time-series (temporal) regression at national (Sudarat Chadsuthi, Modchang, Lenbury, Iamsirithaworn, & Triampo, 2012; Desvars et al., 2011; Joshi, Kim, & Cheong, 2017; Lee et al., 2014; Ward, 2002b; Weinberger et al., 2014) and sub-national levels (Coelho & Massad, 2012; Deshmukh et al., 2018; Matsushita et al., 2018) to assess the effect of climatic variables and forecast leptospirosis outbreaks for humans (n=7) (Sudarat Chadsuthi et al., 2012; Coelho & Massad, 2012; Deshmukh et al., 2018; Desvars et al., 2011; Joshi et al., 2017; Matsushita et al., 2018; Weinberger et al., 2014) and canine infection (n=2) (Lee et al., 2014; Ward, 2002b) (Table 3). Various temporal resolutions ranging from daily to

monthly infection data were used with various timespans ranging from 7-16 years. Most studies included climatic factors such as precipitation, temperature and humidity as predictors (n=8/9) in the models. One study investigated the effect of El-Nino Southern Oscillation (ENSO) components (e.g., sea surface temperature anomaly, southern oscillation index, and oceanic Nino index) on human leptospirosis incidence in New Caledonia (Weinberger et al., 2014). Autoregressive models were used in three studies: human leptospirosis (n=2) (Sudarat Chadsuthi et al., 2012; Desvars et al., 2011) and canine leptospirosis (n=1) (Ward, 2002b). One sub-national study in Philippines employed distributed lag non-linear (quasi-Poisson) model to assess non-linear relationships between rainfall and leptospirosis and the role of flood events (Matsushita et al., 2018).

3.7 Model validation

Overall, model validation procedures to determine model accuracy were described in less than half of spatial modelling studies. Several measures were used to evaluate models including information criteria such as Akaike's information criterion (AIC), Bayesian information criterion (BIC), or deviance information criteria (DIC), Pearson chi-squared goodness-of-fit tests, and Hosmer-Lemeshow test. Data partitioning (e.g., splitting the data into 'training' and 'testing' subsets) was often used to validate the models as well as internal cross-validation (White et al., 2017). The Area Under the Receiver-operator curve (AUC ROC) analysis (C. L. Lau, Clements, et al., 2012; H. J. Mayfield et al., 2018b; Zhao et al., 2016) was applied to determine discriminatory performance and predictive accuracy of the models.

4. Discussion

This study is the first to review the application of spatial analytical methods in the field of leptospirosis epidemiology. Our review demonstrates the potential of spatial-temporal epidemiological approaches to improve our knowledge of human and animal leptospirosis

and its possible applications for assisting future intervention strategies to reduce leptospirosis burden. However, this review has identified a number of methodological limitations of existing studies that hinders their ability to provide a sound evidence base to guide local control efforts to reduce the burden of leptospirosis in humans and animals.

The source and quality of leptospirosis infection data substantially underpins the validity of spatial epidemiological studies. Indeed, our review noted that most studies have utilized leptospirosis notification data obtained from passive surveillance, which is likely to under represent the true incidence; although using notification data could be more feasible compared to conducting cross-sectional eco-epidemiological studies. It is noteworthy to acknowledge important disadvantages when using notification data, particularly for a disease such as leptospirosis, which is prone to being highly underreported. Of note, one concern with leptospirosis case ascertainment is that many endemic countries have limited laboratory capacity to undertake confirmatory diagnostic tests, so that the notification data may be primarily based on rapid diagnostic tests (RDT) or ELISA. Even these tests may not be routinely available throughout the country and this could lead to significant underdiagnosis and underreporting. In addition, other issues including the sensitivity and specificity of the diagnostic methods used and discrepancies in reporting systems may also impede the quality of such notification data. To further compound this problem, we identified several studies that did not clearly state the diagnostic tests or the case definitions used. These issues may greatly affect the clarity and quality of the data and thus lead to uncertainty about the geographical distribution of leptospirosis. This could misguide policy makers when developing strategies to efficiently target interventions to populations and areas at greatest risk. Given these limitations, future studies should carefully deal with the uncertainty in the epidemiological data.

In terms of spatial analysis approach, a considerable number of studies have used visualization techniques to produce morbidity and mortality distribution maps. Indeed, such maps could be useful to assist health authorities to understand the geographical distribution of cases or risks. However, there are some common issues that needs to be carefully addressed when producing maps so that they are not misinterpreted. Besides the quality of data, the validity of the outcome of spatio-temporal analyses is greatly dependant on the spatial scale at which the analysis was performed, the type of data used (point or areal data), and how aggregation of areal data was conducted.

In particular, mapping geographical distribution of *Leptospira* serogroups or serovars identified in humans, host animals, and environment is also of great importance; yet, our review indicates that this is still poorly explored. Such maps could be beneficial to support vaccine development (mainly for animals) and to better design control programs (e.g., identifying key animal sources of human infection to target One Health interventions). Of note, mapping the current distribution and future spread of pathogenic *Leptospira* may provide better understanding on the burden of leptospirosis. Further studies are therefore strongly encouraged to map the distribution of serogroups or serovars at various spatial-scales as it has important implications for understanding patterns of leptospirosis endemicity and aid investigators to generate hypotheses on the potential source(s) of infection (host animals) as some specific serogroups/serovars are linked with specific host animals (e.g., serovars Canicola with dogs, Pomona with pigs, Hardjo with cattle) as well as disease severity and associated socioecological conditions.

Exploring spatial clustering of leptospirosis prior to modeling is fundamental for understanding spatial dependency of cases (Lawson, 2013). Furthermore, investigation of the presence of spatial dependence is a first step for deciding the best modelling approach for quantifying predictors of disease and predictive risk mapping. Our review demonstrates

significant variation in the application of techniques used to test for spatial clustering, which requires systematic analysis as demonstrated by some of the studies reviewed here (C. L. Lau, Clements, et al., 2012; Rood et al., 2017). To detect spatial clustering, both global and local indices of spatial autocorrelation should be estimated, and it is also important to consider the type of the data (areal or point data) when choosing methods. Our review highlights that almost all studies have overlooked the importance of assessing spatial autocorrelation in the residuals of non-spatial models. It also appears that most studies solely evaluated spatial autocorrelation, but when present, did not incorporate it into the modeling framework. Ignoring spatial dependence in the data can give rise to spurious associations, inaccurate and biased parameter estimations and spatial risk predictions (Dormann, 2007; Pfeiffer, 2008).

Another step for exploring spatial dependence involves the utilization of spatial cluster detection techniques; by far the most commonly used by the studies reviewed here was Kuldorff's Spatial Scan statistic (SaTScan). This method allows researchers to estimate the relative risk inside and outside identified geographical clusters of disease by using predefined scanning windows and Monte Carlo simulation (Martin Kulldorff & Neville Nagarwalla, 1995). Despite its simplicity, there was no standard selection of thresholds across studies for the shape and size of the cluster scanning window (~10-50% of the population at risk) as the size and shape selection may depend on the nature of the data and their objectives. All studies assumed that disease clusters were circular, while ecologically, the disease often forms irregularly-shaped clusters (e.g., due to variation in a population or environmental characteristics). The use of circular scanning windows may reduce the chance to detect non-circular shaped clusters. To better detect and deal with irregularity of the disease clusters, alternative cluster detection tools could be used for future studies, such as FlexScan or a

multidirectional optimal ecotope-based algorithm (AMOEBA) (Aldstadt & Getis, 2006; Ramis, Gomez-Barroso, & López-Abente, 2014; Zhu et al., 2016).

Our review shows that large number of spatial modelling studies assessed the association between physical environment (e.g., altitude, vegetation, proximity to water bodies, sewerage systems or waste) and climatic factors on leptospirosis, suggesting the high importance of the environment on leptospirosis transmission, while factors associated with sociodemographic conditions (e.g., urbanization, poverty) and animal hosts appears remain overlooked by many studies. In the context of zoonotic disease control, it is recognized that a One Health approach has greater potential to effectively control disease burden than focusing on human disease alone. Such One Health framework should therefore be accommodated in future spatial models (i.e., the inclusion of animals host factors along with environment predictors and social determinants of health) to provide more comprehensive evidence for decision-making processes.

In terms of modeling methodology, the majority of spatial modelling studies reviewed here used a range of traditional regression models (frequentists) and very few have applied modeling techniques (e.g., Bayesian geostatistics methods) that fully address spatial autocorrelation. A disadvantage when using standard statistical modelling techniques is that they assume independence of observations and do not account for potential spatial dependency between neighbouring locations. When overdispersion or the effect of spatial dependence on the data are ignored, the standard errors could be underestimated and hence increase the risk of Type I errors (Pfeiffer, 2008). In addition, such traditional regression models are not able to identify variation in the relationships between the predictors and capture the complexity of disease transmission. There are several promising methods that could be used in future leptospirosis studies, such as Bayesian geostatistics, geographically weighted regression (GWR) and spatial Bayesian Belief Network (BBN). Recently, Bayesian

548 geostatistics techniques have been widely used in various spatial epidemiological zoonotic
549 diseases studies. This method has advantages over common frequentist regression models.
550 Bayesian approaches are suitable when data are sparse and highly clustered. It allows
551 accounting for spatial autocorrelation and adequately addresses uncertainties in the model
552 design (Cressie, Calder, Clark, Ver Hoef, & Wikle, 2009; P. Diggle & Ribeiro, 2007; P. J.
553 Diggle, Tawn, & Moyeed, 1998). Other methods such as geographically weighted regression
554 (GWR) (Helen J. Mayfield et al., 2018a) and Bayesian Belief Network (BBN) (C.L. Lau et
555 al., 2017; Pittavino et al., 2017) have also been used in a few epidemiological studies in
556 leptospirosis. The former provides opportunity to better deal with spatial non-stationarity of
557 covariates in the models (Fotheringham, Brunsdon, & Charlton, 2002), while the latter has
558 the ability to effectively reveal and describe the complexity of relationships between
559 variables in disease system (Landuyt et al., 2013; Lewis & McCormick, 2012). To help
560 enhance understanding of leptospirosis transmission and predictive maps, further studies
561 should be directed on exploring such non-traditional modeling techniques and incorporating
562 spatial-temporal elements into the models. All of these methods may allow researchers to
563 produce more robust and better predictive risk maps for leptospirosis to better inform health
564 managers on planning leptospirosis control. However, as the models become more complex
565 and more advance modeling techniques being used, it may greatly need considerable time,
566 technical skill requirements and computational capacity. For instance, using Bayesian
567 geostatistical models could take hours or even days to run the model, while some techniques
568 (e.g., spatial BNs) could be much faster and almost instantaneous. Recent study in Fiji offers
569 promising approach to better understand leptospirosis transmission under various socio-
570 ecological scenarios by using spatial Bayesian Networks (H. J. Mayfield et al., 2018b)

571 Assessing the effect of climate variability (e.g. precipitation, temperature, ENSO) on
572 leptospirosis risk allows researchers and public health officials to forecast when outbreaks

may occur. It should be noted that one of the critical limitations of the conventional time-series modeling (e.g., ARIMA) is that it mainly assesses linear relationships of variables within the time series data (Zhang, Zhang, Young, & Li, 2014), while the relationships between variables and infection are commonly non-linear. To better address this non-linearity of associations, some techniques could be used in the future model such as distributed lag non-linear models (DLNM) (Gasparrini, Armstrong, & Kenward, 2010). Given the complexity of leptospirosis infection pathway, future spatiotemporal models of leptospirosis distribution also need to incorporate the joint effects of multiple variables such as climatic and socioecological factors. One potential approach to better incorporate those complexity and enhance predictive capability of leptospirosis forecasting models is machine learning. The application of machine learning algorithms such as Random Forest, Boosted Gradient and Neural Networks, have been demonstrated to have better performance and high predictive ability in several public health studies (Carvajal et al., 2018; Chen et al., 2018; Guo et al., 2017; Hu et al., 2018). Future studies should be directed on exploring such machine learning methods in modeling leptospirosis transmission.

4.1 Framework for the application of spatial analytical tools for leptospirosis studies

We proposed a general framework that could guide for the application of spatial epidemiological methods for future leptospirosis studies (Box 1). In general, there are three key components, including input, spatial analytical processes and output. Note that the first stage (input) is a critical part of the inference as the analytical processes and the usefulness of the outputs (maps) greatly depend on the quality, type and spatial and/or temporal scale of the infection data and attributes. This framework may have potential to be adopted not only for leptospirosis but also other diseases.

4.2 Limitations

Publication bias is an important limitation which should be considered when interpretating our findings. Our review solely relied on published research manuscripts and we did not take into account another types of publications (e.g. theses or dissertations, conference proceedings). In addition, most studies captured by our systematic search came from a limited set of countries; this may reflect substantial issues within the countries regarding the availability of the data due to technical issues (e.g., reporting systems, diagnostic capacity) in many endemic countries (Musso & La Scola, 2013; Schreier, Doungchawee, Chadsuthi, Triampo, & Triampo, 2013), poor public awareness and knowledge on recognizing the disease (Mohan & Chadee, 2011), and variation in surveillance systems (Costa et al., 2012).

5. Conclusions

While the use of spatial and temporal analyses has been greatly appreciated in the field of leptospirosis research, the quality of studies and analytical approaches varied significantly. To better understand the epidemiology and processes underlying leptospirosis transmission, appropriate spatio-temporal techniques should be chosen and applied taking into consideration quality and type of data, the geographical scale of analysis and type of covariates for inclusion. Uncertainty in disease modelling outputs should be carefully considered so that the model outputs can be effectively applied to support leptospirosis control interventions. Future work should be prioritized on optimizing the potential of GIS/RS for developing user-friendly and interactive decision-support system, providing an updateable maps at local and national level at finer resolution as new data become available, and constructing more robust and reliable predictive models that account for spatial and temporal dependencies in leptospirosis transmission from different animal hosts and in different environments.

Acknowledgements

This systematic review was conducted as part of Pandji Wibawa Dhewantara's PhD degree at the School of Veterinary Science, the University of Queensland. PWD received PhD scholarship from Australia Awards Scholarships (AAS) – Department of Foreign Affairs and Trade (DFAT), Australia. The authors have indicated that no explicit funding was received for this work. CLL was supported by an Australian National Health and Medical Research Council (NHMRC) Fellowship (1109035). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest

The authors have declared that no competing interests exists.

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1136 **Table 1.** Summary of approaches used to measure spatial clustering in human, animal, and both human-animal leptospirosis studies

Spatial clustering methods		**N**	**Infection data**		
			Human (n=21)	**Animal (n=13)**	**Both human and animal (n=1)**
Global measures	Moran's I / Global Moran	11	(Cook et al., 2017; Della Rossa et al., 2016; Goncalves et al., 2016; Gracie et al., 2014; Mohammadinia et al., 2017; Mohd Radi et al., 2018; Rood et al., 2017; Soares et al., 2010; Suryani et al., 2016)	(Alton et al., 2009)	(Hurd et al., 2017)
	Geary's c	1			(Hurd et al., 2017)
	Cuzick-Edwards *K*th neighbor test	3		(Hennebelle et al., 2013; R. K. Raghavan et al., 2012; Scolamacchia et al., 2010)	
	Average nearest neighbor	2	(Mohd Radi et al., 2018; Suryani et al., 2016)		

	Knox test	1	(Bennett & Everard, 1991)		
	Semivariogram/Empirical variogram	6	(C. L. Lau, Clements, et al., 2012)	(Alton et al., 2009; R. Raghavan et al., 2011; R. K. Raghavan et al., 2013; R. K. Raghavan et al., 2012)	(Hurd et al., 2017)
Local measures / cluster detection	LISA / Local Moran	3	(Mohd Radi et al., 2018; Rood et al., 2017; Soares et al., 2010)		
	Getis-Ord G*	3	(Hassan & Tahar, 2016; Helen J. Mayfield et al., 2018; Suwanpakdee et al., 2015)		
	Bernoulli/Poisson spatial scan statistics	10	(Cipullo & Dias, 2012; Deshmukh et al., 2018; C. L. Lau, Clements, et al., 2012)	(Alton et al., 2009; da Silva et al., 2006; Hennebelle et al., 2013; Himsworth et al., 2013; Miyama et al., 2018; Nicolino et al., 2014;	

				Sumanta et al., 2015)	
	Poisson/Binomial/Multinomial space-time scan statistics	8	(Gutierrez & Martinez-Vega, 2018; Massenet et al., 2015; Robertson et al., 2012; Sulistyawati et al., 2016; Tassinari et al., 2008)	(Alton et al., 2009; Gautam et al., 2010; Hennebelle et al., 2013; Ward, 2002a)	
	FlexScan spatial cluster test	1			(Hurd et al., 2017)

1143 **Table 2**. Summary of modeling techniques used in eligible leptospirosis studies

Modeling approach		N	Leptospirosis epidemiological data		
			Human (n=31)	**Animal (n=17)**	**Human and animal (n=3)**
Regression	Linear regression/Generalized linear models (GLMs) /Poisson regression/Binomial GLM/Quadratic regression	14	(Ledien et al., 2017; Mohd Radi et al., 2018; Reis et al., 2008; M. C. Schneider et al., 2012; Vega-Corredor & Opadeyi, 2014)	(Biscornet et al., 2017; J. K. Elder et al., 1986; Himsworth et al., 2013; Ivanova et al., 2012; Major et al., 2014; Miyama et al., 2018)	(S. Chadsuthi et al., 2017; Della Rossa et al., 2016; Hurd et al., 2017)
	Logistic regression/multilevel mixed-effect logistic models/multinomial logistic models	17	(Cook et al., 2017; C. L. Lau, Clements, et al., 2012; C. L. Lau, Dobson, et al., 2012; C. L. Lau et al., 2016; Robertson et al., 2012; M. C. Schneider et al., 2012; Tassinari et	(Alton et al., 2009; Ghneim et al., 2007; Himsworth et al., 2013; R. Raghavan et al., 2011; R. K. Raghavan et al., 2013; R. K. Raghavan et al., 2012; Silva et	(S. Chadsuthi et al., 2017)

			al., 2008; Zhao et al., 2016)	al., 2018; Ward et al., 2004)	
	Generalized additive models (GAMs)	3	(Hagan et al., 2016; Reis et al., 2008)	(Bier et al., 2013)	
	Negative binomial (NB)/Zero-inflated negative binomial regression models	2	(M. C. Schneider et al., 2015; Suwanpakdee et al., 2015)		
	Geographical weighted regression (GWR)	5	(Helen J. Mayfield et al., 2018a; Mohammadinia et al., 2017; Mohd Radi et al., 2018; Vega-Corredor & Opadeyi, 2014; Widayani et al., 2016)		
	Generalized linear mixed models (GLMMs)	2	(Tassinari et al., 2008)	(Alton et al., 2009)	
	Boosted regression trees (BRTs)	2	(Ledien et al., 2017)	(White et al., 2017)	
Autoregressive models	Simultaneous Auto Regression (SAR)	1	(Rood et al., 2017)		

Disease distribution modelling	Maximum entropy (MAXENT) Ecological niche models, Genetic Algorithm for Rule Set Production (GARP)	2	(Sanchez-Montes et al., 2015; Zhao et al., 2016)		
Bayesian approach	Integrated Nested Laplace Approximation (INLA) + Stochastic Partial Differential Equations (SPDE); Bayesian inference; Besag, York and Mollie (BYM) model; Spatial Bayesian Networks	4	(Baquero & Machado, 2018; Hagan et al., 2016; Reis et al., 2008; (H. J. Mayfield et al., 2018b))		
Interpolation technique	Kriging	3	(Deshmukh et al., 2018; Dozsa et al., 2016; Goncalves et al., 2016)		
Correlation	Pearson correlation / Spearman's correlation	4	(Gonwong et al., 2017; Gracie et al., 2014; Soares et al., 2010)	(Jean K. Elder & Ward, 1978)	
	Chi-square test	3	(Barcellos & Sabroza, 2001; Goncalves et al., 2016)	(Ghneim et al., 2007)	
	ANOVA/Bivariate analysis	3	(Barcellos & Sabroza, 2000; M. C. Schneider et al.,		

			2012; Suryani et al., 2016)		
	Mallow’s Cp statistics	1		(J. K. Elder et al., 1986)	
Decision analysis	Decision tree analysis	1		(Bier et al., 2012)	

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1152 **Table 3**. Summary of papers dealing with temporal time-series modeling

Reference	Objective	Location (Spatial scale)	Study period (Temporal scale)	Data source	Method(s)	Predictor(s)	Findings
Human leptospirosis (n=7)							
(Weinberger et al., 2014)	To assess the relationships between climate and meteorological variables with leptospirosis cases; to develop a predictive model for timing of leptospirosis outbreaks	New Caledonia (national)	2000-2012 (Monthly)	Laboratory-based passive surveillance notification	Negative Binomial Regression model (NBM), Principal component analysis, Bayesian information criteria (BIC), partial correlations, multivariate analysis, log-transformation, training tests, Serfling approach	Oceanic Nino Index (ONI), sea surface temperature, Southern Oscillation Index (SOI), rainfall, and temperature	Significant associations between leptospirosis incidence and El Nino indices, SST anomalies, and rainfall. SST anomaly could forecast an increase in leptospirosis cases with a 4-month lag.
(Coelho & Massad, 2012)	To examine the correlation between leptospirosis cases with climatic predictors	Sao Paolo, Brazil (sub-national)	1998-2005 (Daily)	Hospital admission report	Negative binomial regression model (NBM)	Rainfall, Max-Min humidity, and temperature	Significant correlation between hospital admissions and rainfall intensity with lag of 14-18 days.

(Desvars et al., 2011)	To describe seasonality of leptospirosis and to test for correlation with meteorological factors	Reunion Island (national)	1998-2008 (Monthly)	Hospital-based passive surveillance notification	Time-series analysis, log transformation, autocorrelation function (ACF), partial autocorrelation (PACF), augmented Dickey-Fuller test, ARIMAX, cross-correlations functions, goodness of fit criterion, AIC, Student's test	Rainfall, temperature, global solar radiation (GSR)	Monthly cases of leptospirosis influenced by cumulated rainfall with lag of 2 months and mean temperature and GSR during the month. Overall, the model could explain 67.7% of the variation of leptospirosis incidence.
(Sudarat Chadsuthi et al., 2012)	To determine and forecast the seasonal pattern of leptospirosis based on historical leptospirosis cases and meteorological data	Thailand (national)	2003-2009 (Monthly)	Passive surveillance notification	Time-series analysis, log transformation, autocorrelation function (ACF), partial autocorrelation (PACF), augmented Dickey-Fuller test, ARIMAX, cross-correlations functions, goodness of fit criterion, AIC	Rainfall, temperature	The role of rainfall and temperature on leptospirosis cases varied spatially across different regions. In the northern region, leptospirosis was driven by rainfall with a lag of 8-months; while in northeastern, rainfall and temperature were found to be associated with leptospirosis incidence with 10-months and 8-months lag, respectively.
(Joshi et al., 2017)	To estimate the influence of climatic variables on leptospirosis cases	Republic of Korea (national)	2001-2009 Daily)	Passive surveillance notification	Time-series analysis, multivariate Poisson generalized linear models, variance inflation factor (VIF)	Daily minimum, maximum, and mean of temperature, minimum relative humidity, daily cumulative rainfall, solar radiation, total hours of sunshine	The minimum temperature, rainfall, and solar radiation were positively associated with leptospirosis cases with a lag of 0-11-weeks.

(Deshmukh et al., 2018)	To determine the association of climatic factors and leptospirosis incidence	Wardha district, India (sub-national)	2015-2016 (monthly)	Hospital-based surveillance	Poisson time-series regression	Minimum-maximum temperature, relative humidity, rainfall	Relative humidity in the month and rainfall in the previous month was the main determinant of leptospirosis incidence in a given month
(Matsushita et al., 2018)	To estimate the relationship between rainfall, flooding and leptospirosis infection	Manila, Philippines (sub-national)	2001-2012 (weekly)	Hospital-based surveillance	Distributed lag non-linear (quasi-Poisson) model, natural cubic spline, quasi-AIC, variance inflation factor (VIF)	Rainfall, flood	Rainfall were correlated with increased hospital admission for leptospirosis at a lag of 2 weeks. This association may partly be explain by flood events.
Animal leptospirosis (n=2)							
(Lee et al., 2014)	To assess and compare regional seasonal patterns in seropositivity for canine leptospirosis	United States (national)	2000-2010 (Monthly)	Laboratory database	Seasonal-trend decomposition analysis based on Loess (STL), logistic regression model	-	Each geographic region has distinctive seasonal patterns for seropositivity. In general, the highest positivity rates were reported in the fall.
(Ward, 2002b)	To describe the seasonal patterns of canine leptospirosis; to assess the role of rainfall on canine leptospirosis incidence	United States and Canada (national)	1983-1998 (Monthly)	Laboratory database	Time-series analysis, autocovariance (ACF), partial autocovariance (PACF), autoregression models, Akaike's information criteria (AIC), cumulative spectrum, Box-Pierce, fluctuation tests, z-distribution, t-statistic,	Rainfall	Rainfall (lag of 3 months) could be used to predict canine leptospirosis incidence in the U.S and Canada.

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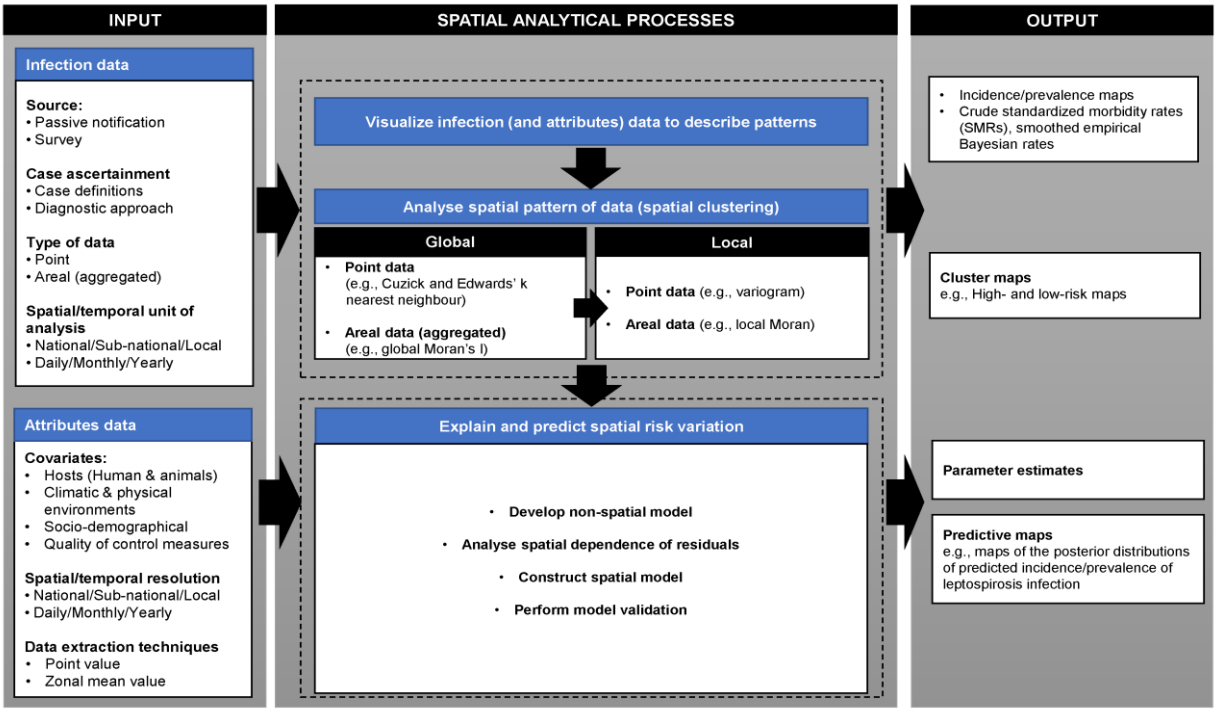
Box 1. General framework for the application of spatial analytical tools for leptospirosis studies



Leptospiral infection data could be obtained from either notification or surveys. Case definitions and methods used to diagnose leptospiral infection should be clearly reported. Prior to the analysis, spatial data type should be determined as point or areal data (by aggregating the data into certain level of spatial unit) as well as the spatial and temporal unit of analysis. Incorporating a wider range covariates (e.g., human and animal hosts, climatic, physical environments, socioeconomic) into the analysis would improve understanding the determinants of the geographical variation of risk of leptospirosis. Geographical and temporal patterns of disease risk is considered influenced by the heterogeneity in hosts (including humans and animals), climatic and physical environments, socio-demographical and also the quality of existing control measures. The spatial and temporal resolutions of those covariates should mirror the resolution of the epidemiological data. Based on the type of spatial data, using GIS tools (e.g., point or zonal mean statistics), the value of each covariate could be sampled.

The basic step of spatial analysis is visualization, which aims to describe patterns in the infection data. Data could be presented as point or choropleth to describe prevalence/incidence or standardized morbidity ratio. To investigate the spatial pattern of the data, according to the type of the data (point or areal data) appropriate statistical tests are carried out to test global (first-order) and local (second-order) spatial clustering. These tests are essential for exploring disease distribution over space (e.g., random or clustered over the space) and to locate high-risk areas. The ultimate objective of spatial and/or temporal analysis is to quantify risks and generate spatial and/or temporal prediction models. This stage employs both non-spatial and spatial regression techniques. All potential covariates are included and selected using fixed-effect regression model. Spatial autocorrelation in the residuals of the final models should be assessed, both by using global and local tests.

Models with the ability to incorporate a spatial dependence component (i.e., Bayesian geostatistical model) are the most relevant to use when spatial autocorrelation is evident. Spatial regression models for risks (prevalence or incidence) could be constructed in Bayesian statistical software e.g. OpenBUGS version 1.4 (Medical Research Council Biostatistics Unit, Cambridge, UK and Imperial College London, London, UK). All models should include all selected covariates as fixed effects plus a geostatistical random effect, in which spatial autocorrelation between locations is modelled using an exponentially decaying autocorrelation function. The outputs of Bayesian models, including parameter estimates and spatial prediction at unsampled locations, are termed as “posterior distributions”. The posterior distributions in terms of the posterior mean and standard deviation then could be mapped using GIS software. This map is known as predictive risk maps. Further details on Bayesian model-based

Figure legends

Figure 1. Search and selection process based on PRISMA framework (Moher, Liberati, Tetzlaff, Altman, & The, 2009). Total of 115 records published until 31 October 2018 were reviewed.

Figure 2. Number of included articles in the review classified by time period. Articles were grouped into three categories based on the epidemiological data used: human, animal, and both human and animal infection data. The use of spatial analytical methods in the field of leptospirosis appears to grow since 1970s.

Figure 3. Distribution of selected papers on spatial and/or temporal analysis of human leptospirosis (A), animal leptospirosis (B), and both human and animal leptospirosis (C).

Figure 4. Covariates included in the models and the proportion of studies that incorporated those variables. Land-use/land cover (e.g., NDVI, type of residence, presence of paddy field), precipitation, altitude, presence of animal reservoirs, population density and poverty were the most common predictors included in the models to estimate risk of leptospiral infection.

Supporting information (filename: Supp_Table S1- S7.docx)

Table S1. Keyword combination used in selection process for the systematic review

Table S2. Summary of the characteristics of studies included in the systematic review

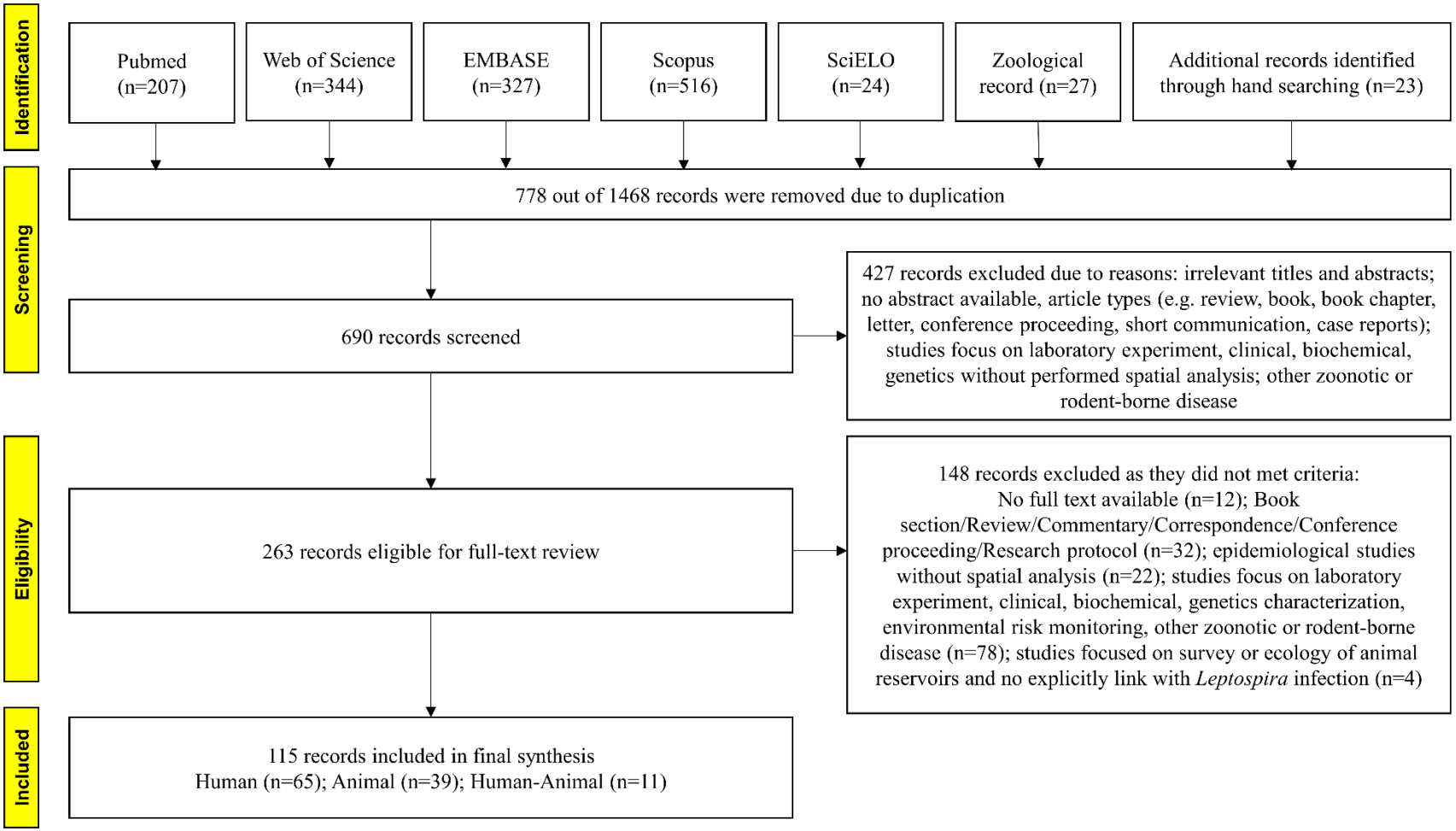
Table S3. Summary of studies on mapping human leptospirosis

Table S4. Summary of studies on mapping animal infection and both animal and human infection data

Table S5**.** Summary of reviewed studies that explored spatial patterns or spatial autocorrelation of leptospirosis

Table S7. Characteristics of studies that used RS data for leptospirosis epidemiology

Table S6. Summary of studies on quantifying risk and modeling on leptospirosis including environmental and socioeconomic predictors used (filename: Supp_Table S6.xlsx)



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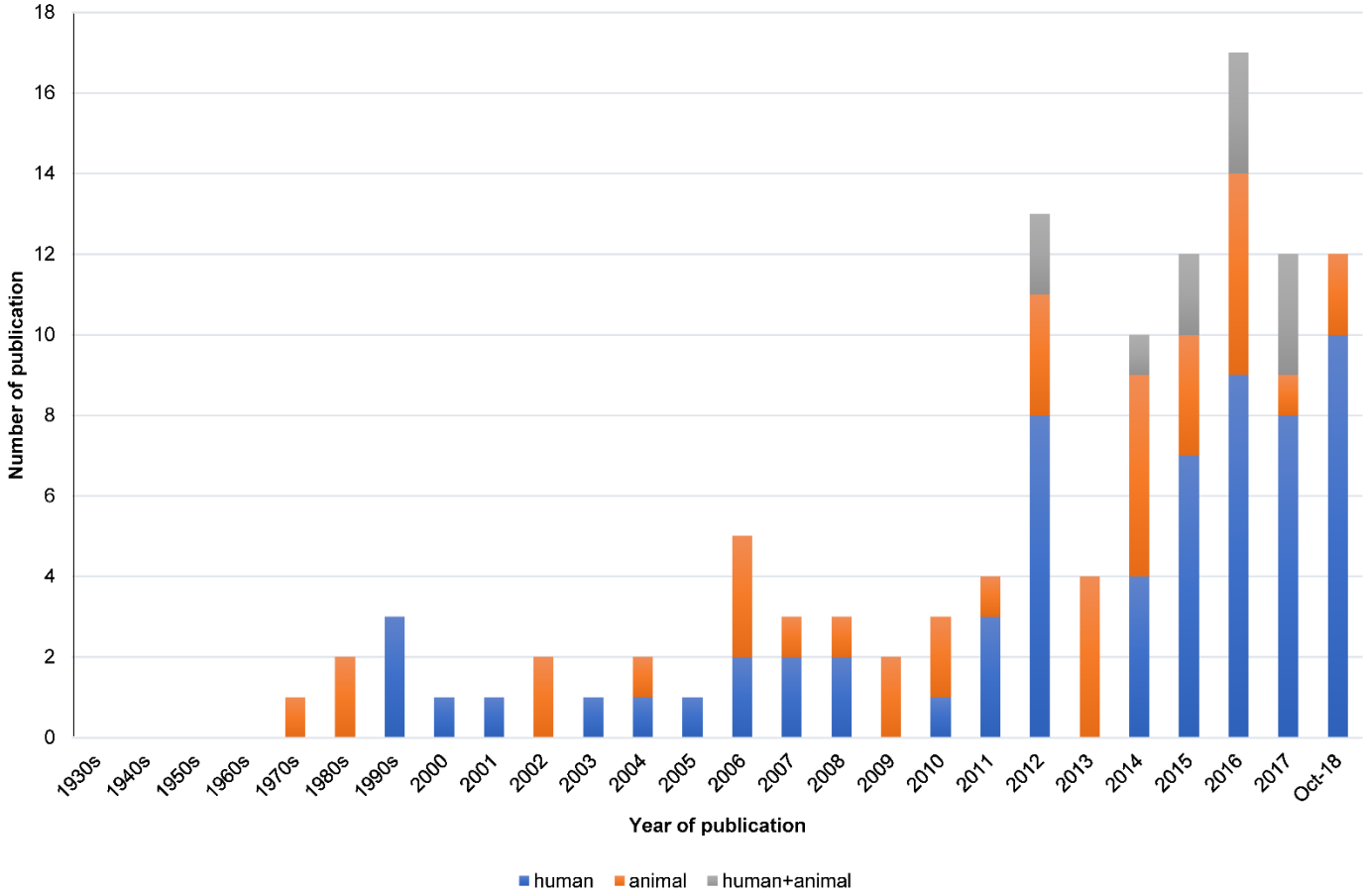

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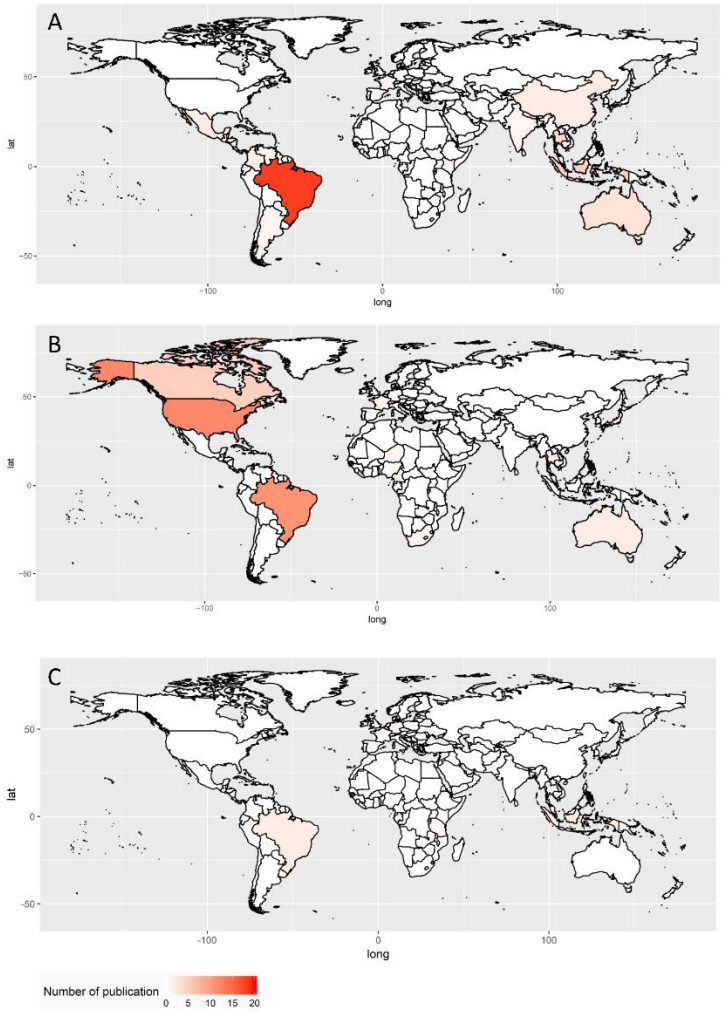

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1216 **Figure 3.** Distribution of selected papers on spatial and/or temporal analysis of human leptospirosis (A), animal leptospirosis (B), and both
1217 human and animal leptospirosis (C).

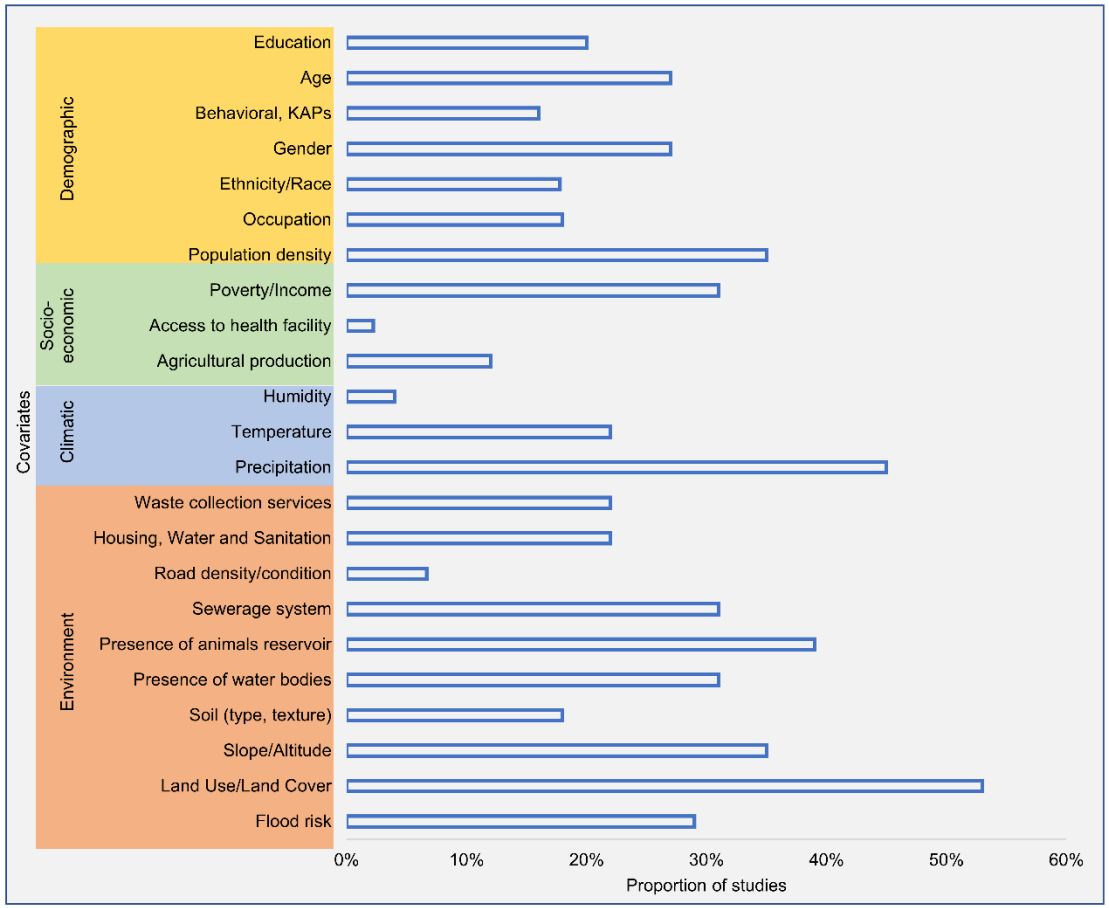

Figure 4. Covariates included in the models and the proportion of studies that incorporated those variables. Land-use/land cover (e.g., NDVI, type of residence, presence of paddy field), precipitation, altitude, presence of animal reservoirs, population density and poverty were the most common predictors included in the models to estimate risk of leptospiral infection.