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A CASE CONTROL STUDY ON FACTORS ASSOCIATED WITH LEPTOSPIROSIS INFECTION AMONG RESIDENTS IN FLOOD-PRONE AREA, KUANTAN: A GEOGRAPHICAL INFORMATION SYSTEM-BASED APPROACH

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ABSTRACT

Background: Leptospirosis, nicknamed "The Great Mimicker", is a zoonotic disease of public health importance, particularly in temperate climate such as Malaysia where seasonal floods occur. This study aims to determine factors associated with leptospirosis transmission such as sociodemographic characteristics, knowledge, attitude and environmental risk factors such as temperature, rainfall, humidity, flood-risk area, distance from waste accumulation sites, land elevation and soil type, as well as predictors of leptospirosis transmission among residents in Kuantan, Pahang by using a Geographical Information System (GIS)-based approach.

Materials and Methods: A population-based case-control study will be implemented in Kuantan, Pahang which utilizes 260 samples, where 130 confirmed cases of leptospirosis and 130 controls who will be randomly selected from neighbours living within 500 metre radius of the cases. A validated interviewer-guided questionnaire will be used to assess respondent's sociodemographic characteristics, leptospirosis status, knowledge, attitude and practice towards leptospirosis. Secondary data will be obtained from the respective departments.

Data Analysis: Descriptive and inferential statistics will be used for data analysis. Knowledge, attitude, practice, and environmental risk factors such temperature, rainfall, humidity mean values, flood risk areas, distance from waste accumulation sites, soil type and land elevation will be mapped by using GIS. Finally, the predictors of leptospirosis will be determined by logistic regression.

Expected Outcome: Due to the transmissibility of leptospirosis increases as the result of flooding, it is expected that the cumulative incidence of cases will come from the flood-prone areas in Kuantan. The majority of the cases could come from areas that have high risk of exposure to environmental factors such as high rainfall density, moderate temperature, high humidity, living in flood-risk areas, low land elevation, nearer to the waste accumulation sites, and moist soil type. It is also expected that eventhough the community might have heard of leptospirosis, the level of KAP might be low due to the increasing national incidence of the infection.

Keywords: Leptospirosis, associated factors, seasonal floods, Kuantan, GIS

1.0 Introduction

Leptospirosis is a worldwide zoonotic disease of great public health importance. The causative microorganism is the pathogenic *Leptospira interrogans*. Its natural reservoirs include rodents, cattle, pigs and canines, which are common animals found in the community setting. The infection is transmitted directly through exposure of infected animal urine or indirectly through contaminated soil or water (de Araújo et al., 2013). Seasonal floods provide suitable medium for leptospirosis transmission, where the water can easily be contaminated.

Pahang, an east-coast state, is exposed to the monsoon season, which usually occurs at the end of the year. Non-stop rainfall in such high area (Sungai Lembing and Kampung Panching) results in increased water level in the river below their level such as Sungai Isap and Sungai Kuantan, which leads to flooding. This is made worst by heavy tides and the shallow section of Kuantan's river estuary and poor drainage system (Department of Irrigation and Drainage, DID, 2012). When flood occurs, the transmission of leptospirosis becomes much evident, as it is transmitted via breaks in skin and mucous membrane due to injuries sustained during evacuation process or even existing wounds on a person.

The incidence of leptospirosis in Malaysia is increasing in trend, ranging from 2 to 6.8 per 100,000 population from 2006 till 2010, with case fatality rate of 2.3 to 4.1% (Lim et al., 2011). This is due to leptospirosis being an infectious disease of various clinical spectrum, ranging from flu-like illness to full-blown sepsis, and patients tend to come at a later stage of the illness. Moreover, there is a tendency to overlook or even misdiagnose the disease as mild flu or dengue at the hospital setting. Furthermore, there have been 238 confirmed cases of Leptospirosis in Pahang state of the year 2014, of which 29 cases or 12.2% of the cases were from Kuantan district. There is an increment of 13.6% of the total cases during the same epidemiological week period compared to last year, where 22, or 10.8% out of 204 reported cases were from Kuantan (Pahang State Health Department, PSHD, 2014).

Detection of the disease is paramount to prevent its transmission. There are many methods used by epidemiologists, one of them is using GIS. GIS is used to map the disease distribution accurately has become a powerful tool to assist in epidemiological studies (Herbreteau et al., 2006). The use of GIS has enabled researchers to correlate environmental risk factors with geospatial data over a larger scale, while minimizing manpower use in field work (Barcellos and Sabroza, 2001). What has made GIS so popular and appealing is the fact that the spatial referencing of information can be organised into maps, with automated mapping technology used to perform the normal operations of database management (subset extraction, intersection, combination, appending, etc.) in a map form, and displaying results in an intuitively understandable manner (Longley, Goodchild, Maguire and Rhind, 2005). This is useful in seasonal flood-prone areas where predicting trends and intervening early are useful for community-based disease prevention (Lau, Clements, Skelly, Dobson and Weinstein, 2012). GIS can be composed of multiple features and surfaces which can be freely edited according to individual needs. Each geographical object in a layer such as city, river, lake and district is called a feature, while surfaces are composed of numerical values such as temperature and rainfall (Ormsby, Napoleon, Burke, Groessl, and Feaster. 2001). In addition, GIS has the ability to determine locations based on geographical x, y coordinates.

Environmental risk factors significantly associated with leptospirosis are flooding in the past 2 weeks, presence of stagnant water in the surrounding house, poor sewer conditions, poor house sanitation, existence of rats, and contact with owned domestic animals (Sakundarno et al., 2014). Flood risk areas comprise of one of the layers in GIS mapping. It it obtained by digitizing polygons in which low terrain slope and convergence of rainfall water increase the likelihood of floods occurring (Barcellos et al., 2001). On the other hand, solid waste accumulation is important as a marker for transmission of leptospirosis by rodents, however it is difficult to get the true distribution of rodents in the population.

Cases of leptospirosis could be mapped on the GIS to obtain a geographical distribution of the cases and its relation with the environmental factors. Thus, correlation between the cases and its environmental risk factors can be determined. A study has shown that a geographically-determined waste accumulation area is statistically significant when plotted against the leptospirosis cases (Barcellos et al., 2001). The incidence rate is highest at 78.29 per 100,000 inhabitants for those who live between 250 to 500 metres from the waste accumulation sites. In the same study, those who lived in flood-risk area have been shown to have higher incidence rate of leptospirosis, at 42.05 per 100,000 inhabitants as compared to those who lived outside the flood-risk area at 19.75 per 100,000 inhabitants, and this difference is statistically significant (Barcellos et al., 2001). In addition, Lau et al. (2012) also describe the relationship between soil type and land elevation with leptospirosis cases.

When GIS is mapped and combined with the factors in study, risk stratification can be done. A study was done in Nicaragua shows that soil type was statistically significant association with the cumulative incidence rate of leptospirosis (Schneider et al., 2012). Figure 1 and 2 shows how GIS was used to map the results in the said study:

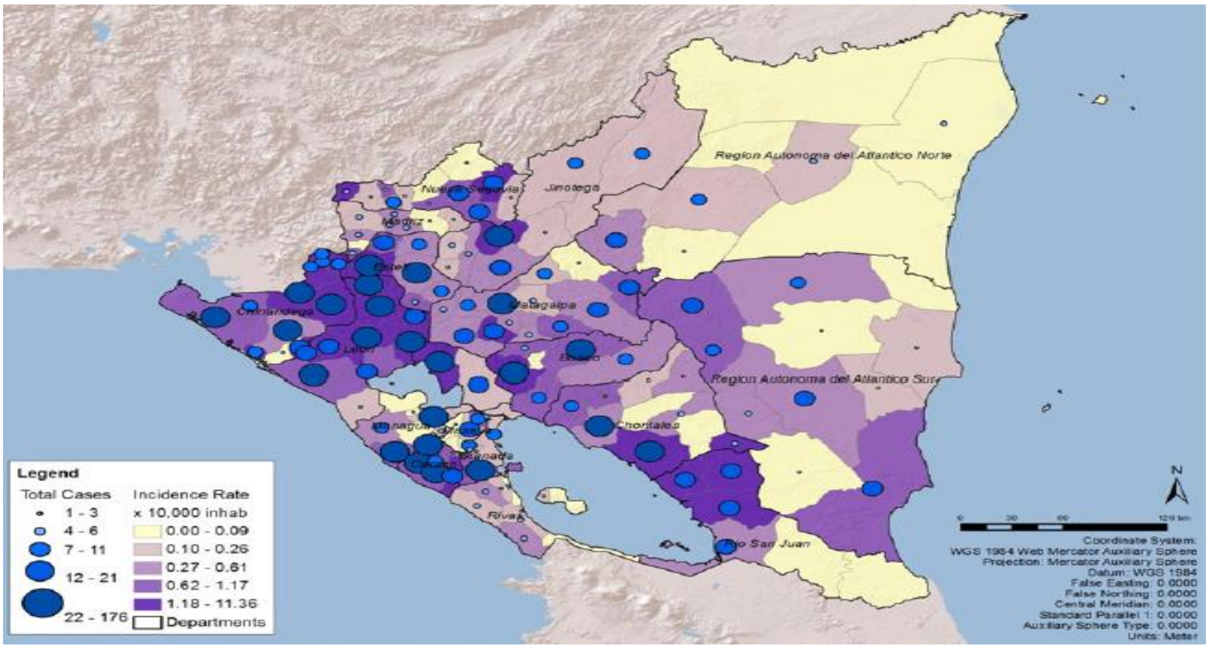


Figure 1: Total number of cases of leptospirosis, cumulative incidence rate per 10,000 population by municipality, Nicaragua, 2004–2010. Taken from Schneider et al, 2012

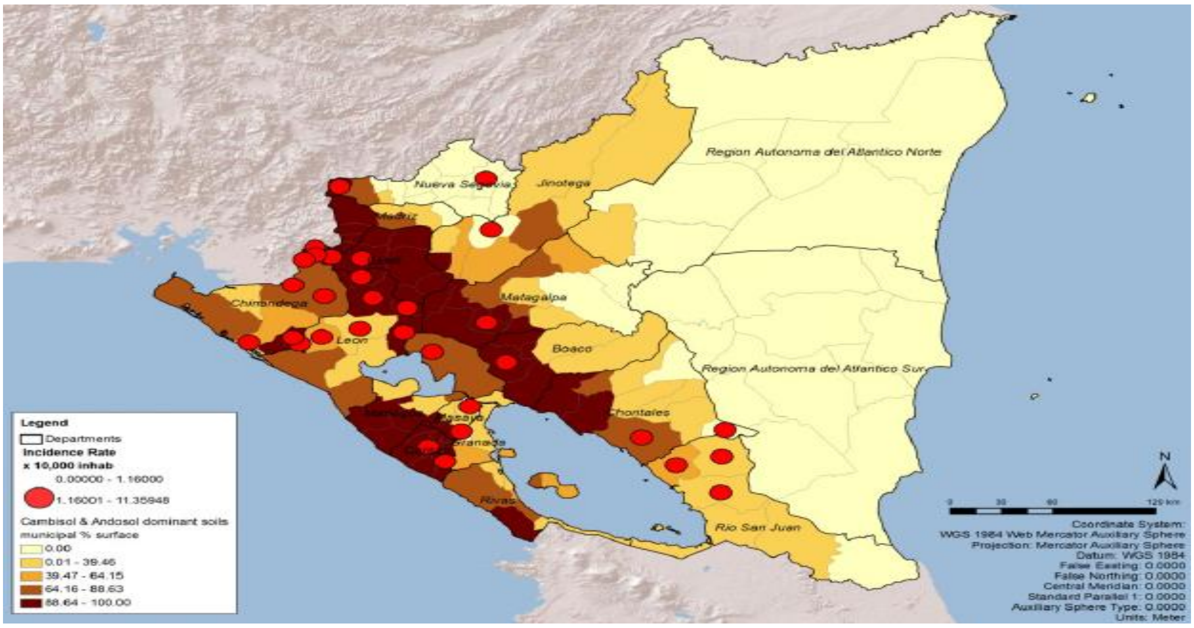
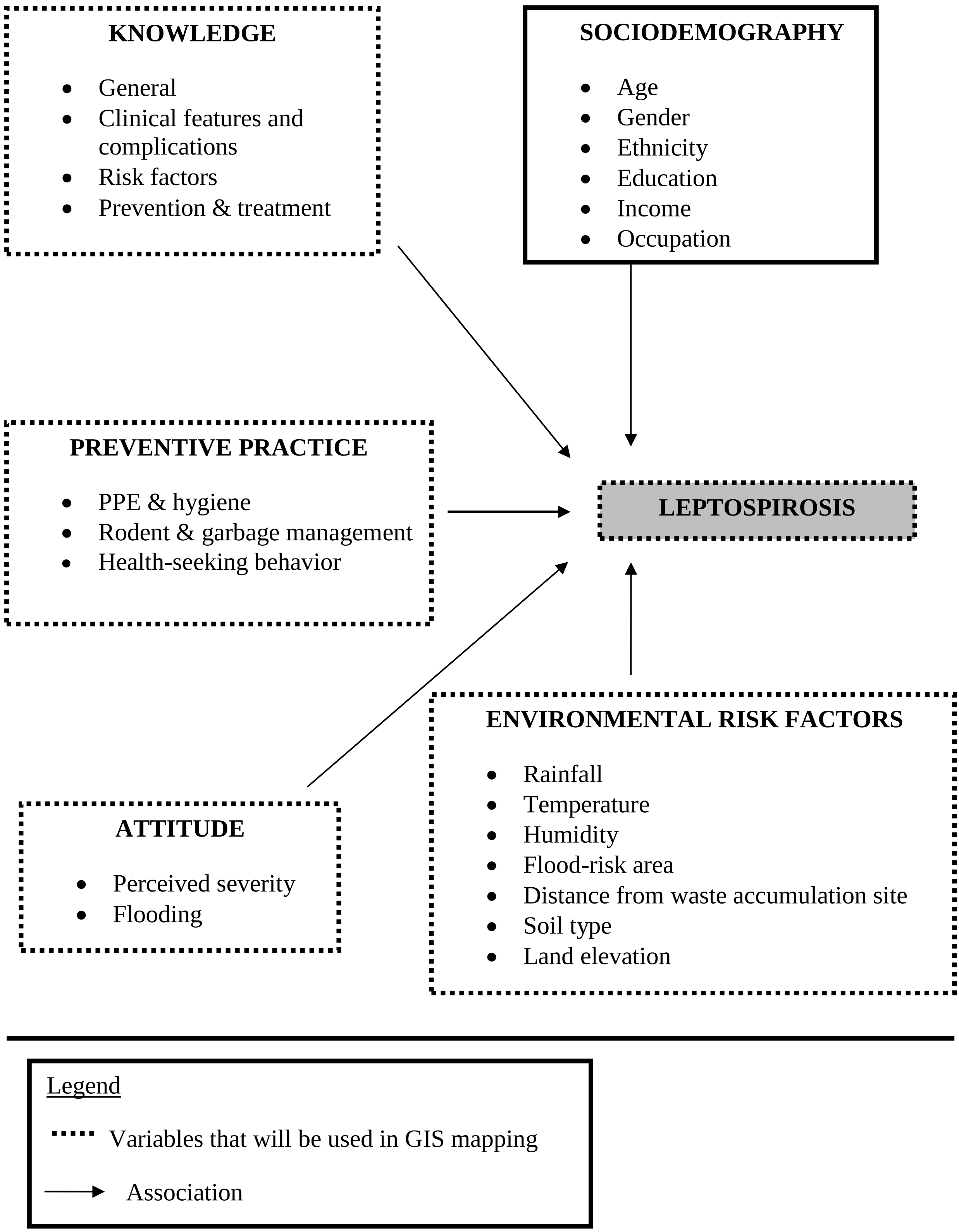


Figure 2: Critical areas for leptospirosis define by incidence rate and percentage of soil with Cambisol and Andosol, by municipality, Nicaragua, 2004–2010. Taken from Schneider et al., 2012)

Due to flooding being a natural disaster and its association with disease transmission, this study aims to uncover the risk factors towards leptospirosis infection by using GIS.

2.0 Conceptual Framework



3.0 Materials and Methods

3.1 Study Location

Kuantan is one of the district in Pahang, and also the capital city of Pahang. It covers an area of 2,960 kilometres per square feet, or approximately 8.2% of the total area of Pahang. It is further divided into 6 sub-districts, which are Kuala Kuantan, Ulu Kuantan, Ulu Lepar, Penor, Beserah and Sungai Karang. During recent years, issues of overpopulation and inappropriate solid waste disposal, continues to be the main contributing factors of water and land pollution in the area (DID, 2012). The outcome of this in the long-run is the occurrence of both natural and human-induced floods, and increased risk for communicable disease transmission.

3.2 Study Design

Population-based case-control study design

3.3 Study Period

April 2015 to December 2015

3.4 Sampling

3.4.1 Study Population

Residents in Kuantan, Pahang

3.4.2 Sampling Population

Inclusion criterias;

<u>Cases</u>
All probable and confirmed cases of leptospirosis aged 18 years and above from January 2014 to April 2015 that meets the standard case definition in Malaysia (MOH, 2011) and based on notification lists gathered from government and private health clinics, as well as government and private hospitals. The definition of probable and confirmed case is as below:

1. Probable Case

A clinical case AND positive ELISA/other Rapid tests. A clinical case is defined as follows;

A case that is compatible with the following clinical description:
Acute febrile illness with history of exposure to water and/or environment possibly contaminated with infected animal urine with ANY of the following symptoms:

- Headache
- Myalgia particularly associated with the calf muscles and lumbar region
- Arthralgia

- Conjunctival suffusion
- Meningeal irritation
- Anuria or oliguria and/or proteinuria
- Jaundice
- Hemorrhages (from the intestines and lungs)
- Cardiac arrhythmia or failure
- Skin rash
- Gastrointestinal symptoms such as nausea, vomiting, abdominal pain, diarrhea

2. Confirmed case

A confirmed case of leptospirosis is a suspected OR probable case with any one of the following laboratory tests:

- Microscopic Agglutination Test (MAT), For single serum specimen - titre 1:400. For paired sera - four fold or greater rise in titre
- Positive PCR (samples should be taken within 10 days of disease onset
- Positive culture for pathogenic leptospires (blood samples should be taken within 7 days of onset and urine sample after the 10th day)
- Demonstration of leptospires in tissues using immunohistochemical staining (e.g. in post mortem cases)
- In places where the laboratory capacity is not well established, a case can be considered as confirmed if the result is positive by two (2) different rapid diagnostic tests.

Cases that require confirmation are:

- Hospitalized cases
- All suspected leptospirosis death cases

<u>Controls</u>
Neighbours without being diagnosed as confirmed and probable cases of leptospirosis during the study period, who reside within 500 metres from the house of the cases.

Exclusion criterias;

- Those who are deaf or mute

Unmatched 1 case to 3 controls will be used in this study.

3.4.3 Sample Size

The sample size estimation is based on Sample Size Determination in Health Studies by Lemeshow and Lwanga (1990). Hypothesis test for an odds ratio formula is used. Using the formula by Lemeshow and Lwanga (1990);

$$n = \frac{\left\{ z_{1-\alpha/2}\sqrt{2P_2^*(1-P_2^*)} + z_{1-\beta}\sqrt{P_1^*(1-P_1^*) + P_2^*(1-P_2^*)} \right\}^2}{\left(P_1^* - P_2^*\right)^2}$$

Where
n = Sample size estimate
$Z_{1-\alpha/2}$ = standard error associated with 95% confidence interval = 1.96
$Z_{1-\beta}$ = standard error associated with 80% power = 0.842
P_1^* = proportion exposed in cases i.e.

$$= \frac{(OR)P^*_2}{(OR)P^*2 - (1-P2^*)}$$

P_2^* = proportion exposed in controls

The chosen sample size estimation is based on the exposure status, in this case swimming which is contact with water, and the illness (Koay, Nirmal, Noitie, and Tan, 2004). It is also because one of the hypotheses is environmental risk factor as the significant predictor of leptospirosis. The calculation below is based on a study on an outbreak investigation in Beaufort, Sabah, Malaysia, using a case control design (Koay et. al., 2004).

$$N = \frac{\{1.96\sqrt{2(0.33)(1-0.33)} + 0.842\sqrt{0.50(1-0.50)+0.33(1-0.33)}\}^2}{(0.50-0.33)^2}$$

= 129
= 130 samples

Thus, 130 samples are needed for case and 390 samples for control group, based on the ratio of one case to three controls.

3.4.4 Sampling Technique

Stratified proportionate random sampling will be used in this study. First, list of flood-prone areas with list of resident areas affected by flood in Kuantan (as strata) will be obtained. The strata are based on their geographical location. From each stratum, proportionate sampling of the houses will be utilized by simple random sampling method. All the samples which fit in the inclusion criteria will be chosen as the final samples. All random sampling will be done using table of random number.

With proportionate stratification, the sample size of each stratum is proportionate to the population size of the stratum. Strata sample sizes are determined by the following equation :
nh = (Nh / N) * n

where nh is the sample size for stratum h, Nh is the population size for stratum h (7000 in Sg. Isap, Kuantan), N is total population size (500,000 in whole Kuantan), and n is total sample size (130 as calculated above)

= (7000/500,000) *130
=1.82 per stratum or 2 respondents per stratum of resident area affected by flood.

3.5 Instrument

A questionnaire on sociodemographic characteristics, leptospirosis status, as well as knowledge, attitude and practice (KAP) is adapted from questionnaires made by Mohd Rahim et al. (2012) and de Araujo et al. (2013). The questions were also constructed based on standard guidelines (MOH, 2011; WHO, 2003). It consists of 51 items excluding part I and II. Part I contains the sociodemographic characteristics such as date of birth, age, gender, ethnicity, education, income and occupation. Part II encompasses leptospirosis status of the respondent, including details regarding the diagnosis and symptomatology. Part III covers 25 knowledge items which is divided into 4 subtopics which are general, clinical features and complications, risk factors and prevention and treatment. The answer options for part II are either true/yes or false/no. A score of “1” will be given for each “true/yes” answer, and “0” for “false/no” answer. Part IV consists of 12 attitude items, including subtopics of perceived severity of the disease and flooding. Part V covers preventive practices that includes 14 items, and divided into 3 subtopics which are PPE & hygiene, garbage & rodent control, and health-seeking behavior. A 5-point likert scale (strongly agree/agree/not sure/not agree/strongly not agree) is used for both part IV and part V. A score of equal or more than 75% indicates good knowledge, while below 75% indicates poor knowledge (Mohd Rahim et al., 2012).

For positive attitude items in part IV, scores of “4”, “3”, “2”, “1” and “0” for “strongly agree, “agree”, “not sure”, “strongly not agree” will be given, respectively. For negative attitude items, the above scoring system is reversed. A score of equal or more than 75% indicates unsatisfactory practice, while below 75% indicates unsatisfactory attitude (Mohd Rahim et al., 2012).

For good preventive practice items in part V, scores of “4”, “3”, “2”, “1” and “0” for “always”, “often”, “sometimes”, “seldom”, and “never” will be given, respectively. A score of equal or more than 75% indicates satisfactory practice, while below 75% indicates unsatisfactory practice (Mohd Rahim et al., 2012).

A pre-test among 30 residents in the study location will be conducted before the actual research. Then, the questionnaire will be reviewed by a panel of experts which includes public health medicine specialists.

Internal consistency will be evaluated by using Cronbach’s alpha coefficient for each scale. A Cronbach’s alpha of equal or more than 0.7 indicates good internal consistency (Tavakol and Dennick, 2011). After that, the final, revised version of the questionnaire will be developed for the actual research. It will be translated into Malay language which is the mother tongue of the residents.

The Garmin tool, with combination of google maps via smartphone, will be used to get the geographical coordinates (latitude and longitude) of the houses of the respondents. The coordinate will be input to the GIS software for the case distribution.

3.6 Validity and Reliability

The content and face validity of the questionnaire will be assured by reviews by experts in Public Health Medicine. Reliability will be assured by test-retest, wherea pilot study is going to be done to the community of a different location. Cronbach's alpha will be analyzed for the questionnaire for reliability in terms of internal consistency.

Bias, a type of systematic error, is expected such as selection bias. Selection bias could be in the form of neyman or late-look bias and information bias such as recall and interviewer bias. Ways to avoid selection bias include using same criteria for selecting cases and controls and obtaining high participation rates. On the other hand, information bias could be reduced by masking the interviewer and study subjects of the research hypothesis and carefully designing the study questionnaire.

3.7 Method of Data Collection

Data for this study will be obtained via both primary and secondary sources. Primary data would be in the form of an interviewer-guided questionnaire. The interviewers consist of the researcher and enumerators. The enumerators will be trained by the researcher to ensure reliability and minimize inter-interviewer variations. An official letter of permission for data collection will be sent to the head of Jawatankuasa Kemajuan dan Keselamatan Kampung (JKKK) and other relevant authorities. After the permission is granted and list of houses is obtained from the head of JKKK and relevant authorities, data collection will be carried out. A written consent will be obtained from the respondents before the interview is carried out. The interview will be conducted in an average of 15 minutes for each respondent, and all questions must be answered. The geographical location of all of the houses which are chosen as the sampling frame will be determined via geographical coordinates which are the latitude and longitude by using garmin and google maps.

Secondary data is obtained for all the cases, and environmental risk factors such as temperature, rainfall, humidity, waste accumulation sites and flood-risk area. Data on cases will be obtained from the PSHD from January 2014 until latest data. Data on temperature, rainfall and humidity will be obtained from the Malaysian Meteorological Department website, while flood-risk area map will be obtained from the DID Malaysia. On the contrary, data on waste accumulation sites are identified from Alam Flora Sdn Bhd., while data of soil type will be obtained from Pahang Agriculture Department. In addition, data on land elevation will be obtained from the department of surveying and mapping of Pahang. All of these data will be mapped in GIS software, overlayed and analyzed. This is to get a visual depiction of association between environmental risk factors and incidence of leptospirosis based on the respective geographic locations.

4.0 Data Analysis

Data will be analyzed using Statistical Package for Social Science (SPSS) version 22.0. All continuous variables will be described using mean (SD), whereas categorical data will be as frequency (%). Appropriate statistical tests will be done according to the variables tested. For categorical data, analysis will be done using chi square. For continuous data, either independent sample t-test or Mann-Whitney U test will be done depending on the normality of the data. Inferential statistics will be used to measure the association between the variables. For predictors, logistic regression will be used as regression analysis. α-level will be set at 0.05. The mean values of knowledge score, attitude score, temperature, rainfall, humidity, practice score, flood risk areas, waste accumulation sites, soil type, land elevation and leptospirosis cases will be mapped using ArcGIS software version 9.3.

5.0 Expected Outcome

Due to the transmissibility of leptospirosis increases as the result of flooding, it is expected that the cumulative incidence of cases will come from the flood prone areas in Kuantan. The majority of the cases could come from areas that have high risk of exposure to environmental factors such as high rainfall density, moderate temperature, high humidity, living in flood-risk areas, low land elevation, nearer to the waste accumulation sites, and moist soil type. It is also expected that eventhough the community might have heard of leptospirosis, the level of KAP might be low due to the increasing national incidence of the infection.

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Declaration

No conflict of interest is declared.

Authors contribution

Author 1: Literature Review, preparing Research Proposal and executing the research activities

Author 2: Contributing in methodological aspects, planning the research activities and analysis aspect of this research

Author 3: Contributing in methodological and analysis aspects of the research.

Author 4: Contributing in the methodology of the GIS component of the research

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