Modeling malaria in southernmost provinces of Thailand: A two-step process for analysis of highly right-skewed data with a large proportion of zeros

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Abstract

Background

Malaria remains a serious health problem in the southern border provinces of Thailand. The issue areas can be identified using an appropriate statistical model. This study aimed to investigate malaria for its spatial occurrence and incidence rate in the southern provinces of Thailand.

Methods

The Thai Office of Disease Prevention and Control, Ministry of Public Health, provided total hospital admissions of malaria cases from 2008 to 2018, which were classified by age, gender, and sub-district of residence. Twenty-four sub-districts were excluded since they had no malaria cases. A logistic model was utilized to identify spatial occurrence patterns of malaria, and a log-linear regression model was employed to model the incidence rate after eliminating non-cases.

Results

The overall occurrence rate was 10.9% and the overall median incidence rate was 431 cases per 100,000 population. Malaria occurence peaked at young adults aged 20–29, and subsequently fell with age for both sexes, whereas incidence rate increased with age for both sexes. Malaria occurrence fluctuated, with the largest peak in 2008 and the lowest in 2018, while the incidence rate decreased. The area with the highest malaria occurrence and incidence rate was remarkably similar to the area with the highest number of malaria cases, which were mostly in Yala province's sub-districts bordering Malaysia.

Conclusions

Malaria is a serious problem in forest-covered border areas. The correct policies and strategies should be concentrated on in these areas, in order to address this condition.

Background

Malaria has been a plague on humanity since antiquity and continues to be so now. It is caused by Plasmodium protozoan parasites and spread by Anopheles mosquitoes [1]. In the 87 developing countries [2] about half of the world's population lives in high-risk malaria transmission zones, especially in tropical and subtropical rural areas. More than 200 million new cases of malaria are recorded each year, with over 400,000 deaths [3]. Southeast Asia contributes about 6% and 7% of global new cases and deaths, respectively, per year, making it the second-largest contributor nation to the global malaria burden [3].

In Thailand, the occurrence and transmission of malaria remain high along the international borders with Cambodia, Myanmar, and Malaysia [4–6]. There is significant geographical heterogeneity in the spatial distribution of malaria incidence, with some regions having little or no incidence of malaria, while other regions remain endemic, especially the rural forest and forest fringe areas. The majority of cases were people who worked in forests, orchards, rubber plantations, and farms [7–8]. Over 13 million people in Thailand (19% of the total population) are currently at risk for malaria and more than 200,000 live in focal active malaria areas [9].

The incidence rate of malaria in Thailand has dropped significantly. Malaria-free status has just been declared in 35 of Thailand's 77 provinces [10]. Despite this achievement, malaria continues to be concentrated along Thailand's borders, making the effort to eradicate the illness much more difficult. The northeast, bordering Lao PDR and Cambodia (especially Ubon Ratchathani and Sisaket provinces), the west, bordering Myanmar (particularly Tak province), and the south, bordering Malaysia (specifically Yala province) are the three main hotspots of malaria transmission in Thailand [11–12]. Malaria occurs in border areas as a result of unregulated migration [13–15]. The area is thickly forested, which serves as a breeding ground for malaria vectors. Due to the remoteness of these places, malaria control might be challenging. Yala's southern half borders Malaysia's Kedah and Perak [16], and is also affected by the unrest in Thailand's southernmost provinces [17]. Malaria incidence has primarily been studied on Thailand's western and eastern borders with Myanmar and Cambodia, while research on malaria in Thailand's southern border region with Malaysia is still scarce.

Since the number of malaria cases in Thailand has decreased and the distribution of cases at sub-district levels is becoming increasingly sporadic as areas progress towards elimination [18–19], the excess of zero cases is an analytical challenge. Excessive zeros commonly occur in many application fields of statistics, including ecology, environmental science, biostatistical, and epidemiological research. The high proportion of zeros can lead to overdispersion, and this means a disagreement between the data and the assumed distribution. In other words, we have more zeroes in our data than the proposed distribution could reasonably explain. The zero-valued data should not be removed from the analysis. In addition, having a large proportion of zeros could indicate an important condition under study. Therefore, in this study, we propose a method to analyze highly right-skewed data distributions with a large proportion of zeros using a two-step approach, in this case study to identify the incidence of malaria in each sub-district adjusted for gender, age group, and year.

Methods

Study setting

The southernmost provinces of Thailand have long experienced political and social unrest that has hampered malaria control activities. The four southernmost provinces, namely Songkhla, Pattani, Yala, and Narathiwat (Fig. 1), cover a total land area of 18,330 square kilometers and are located approximately 1,000 kilometers south of Bangkok. The Songkhla, Yala, and Narathiwat provinces share a border with Malaysia at various points. These four provinces consist of 49 administrative districts and 377 sub-districts. As of 2013, these four provinces had a combined population of over 2.7 million. The climate in the southernmost provinces of Thailand is characterized as tropical. The temperature in this area ranges from 20 degrees Celsius to 37 degrees Celsius, with an average of 27 degrees Celsius. Also, the area has mountain ranges and rainforest jungles. The forests and mountains present a breeding ground for mosquitoes and other disease-transmitting insects. This area has consistently been among the provinces with the highest malaria morbidity in Thailand.

Data sources and management

Hospital admissions for malaria, classified by age, gender, date of admission, sub-district of residence and citizenship were available from the Office of Disease Prevention and Control, Ministry of Public Health. The Department of Provincial Administration in Thailand's Ministry of Interior has resident populations for the citizens by age, gender, sub-district and year.

Total hospital admissions in 2008–2018 and populations of sub-districts (in 2013) were used for data analysis. These data can provide malaria incidence rates and the incidence rates are computed by dividing numbers of disease cases by corresponding populations at risk.

The effects of gender, age, year and sub-district were used to predict malaria incidence. Gender and age were grouped together into 16 levels (with eight levels of age in years: 0–19, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, and 70+). There were 377 levels of sub-district (with 127 sub-districts of Sonkhla, 115 sub-districts of Pattani, 58 sub-districts of Yala, and 77 sub-districts of Narathiwat) and 11 levels of year included in the analysis.

We compute incidence rates for malaria in cells combining year, gender-age-group and sub-district. In total there are 66,352 cells (11 years × 16 gender-age groups × 377 sub-districts).

The occurrence in cells that combined year, gender, age group, and sub-district, omitted 68 sub-districts that had no instances for 11 years in a row. In the study area, there were 54,384 cells (11 years old, 16 gender-age groups, and 309 sub-districts), with an incidence rate of 48,436 in cells combining year, gender-age-group, and sub-district that had no instances. There were also 5,948 cells with nonzero incidence rate.

Statistical models

In many cases, the Poisson model for disease counts fails due to excess variation in the data, in which case biostatisticians prefer to fit a negative binomial model with an over-dispersion parameter, θ, where smaller values of θ correspond to greater dispersion. In this case, the fit of a negative binomial model with a very small value of θ is still poor when there are many zeros in the data cells, in which case biostatisticians use zero-inflated or hurdle models.

In this study, we propose an alternative model. The model simplifies fitting the zero-inflated model by separating incidence into occurrence and incidence rate. This allows separate models to be fitted to the data for these two outcomes, which could have different predictor patterns. An occurrence is coded as 1 if the cell contains at least one positive outcome, and 0 otherwise. The incidence rate is the number of cases divided by the population, given that there is at least one.

An occurrence can be modeled simply using logistic regression. The model was fitted using the following equation:

$$ln\left(\frac{p_{ijkl}}{1 - p_{ijkl}}\right) = \mu + \alpha_i + \beta_j + \delta_k + \gamma_l$$

where p_{ijkl} denotes the outcome probability in a combination of predictive factor levels. The terms α_i, β_j, δ_k and γ_l thus represent effects of age-gender, year, sub-districts and cell population. The cell population was included as an extra predictor for the possibility that cells with relatively large populations are more likely to have an occurrence. In this model, the outcome probability is expressed as the following equation:

$$p_{ijkl} = \frac{1}{1 + exp(-\mu - \alpha_i - \beta_j - \delta_k - \gamma_l)}$$

The incidence rate can be modeled using a log-linear regression model, in which the logarithms of incidence rates in cells have normal distributions. The log-linear model was fitted using the following equation:

$$\ln\left(\frac{n_{ijk}}{P_i}\right) = y_{ijk} = \mu + \alpha_i + \beta_j + \delta_k$$

In this model, P_i is the population in a sub-district, and n_{ijk} is the corresponding number of reported cases in each sub-district *k* and gender-age group *i* of the year *j*.

We used "sum contrasts" [20] instead of conventional "treatment contrasts" where the first level is left out of the model to be the reference. This method allows us to compute the estimate and the 95% confidence interval of the occurrence and incidence rates for levels of each predictive factor in the models [21]. A confidence interval plot can be used to divide levels of a predictor into three groups, depending on the placement of these intervals completely above, around, or below a specified level. The thematic map was created by classifying sub-districts according to whether their malaria occurrence is above or below the overall mean, while another thematic map was created by classifying sub-districts according to whether their malaria incidence rate is above or below the overall median.

To assess the accuracy of model prediction, the Receiver Operating Characteristic (ROC) curve from logistic regression was drawn [22]. The area under the ROC curve (AUC) measures the performance of a model and represents model accuracy. Linear regression models assume that errors are normally distributed, and this assumption is best assessed by a quantile-quantile (Q-Q) plot of studentised residuals.

Results from the models are shown as confidence interval plots and thematic maps. All statistical analysis and graphical displays were done using the R program version 3.4.4 [23].

Results

Total hospital admissions range from 0 (68 sub-districts) to 4,077 times (Balah sub-district in Yala), with high numbers in mountainous areas along the southern border with Malaysia. The populations of sub-districts ranged from 1,678 (Ta Che sub-district in Yala) to 148,284 (Hat Yai sub-district in Songkla) (Fig. 2).

The 68 sub-districts with no cases for a consecutive 11-year period were omitted. Only 5,948 records out of 54,384 in the study region (11 years old, 16 gender-age groups, and 309 sub-districts) had a malaria occurrence, resulting in a 10.9% occurrence rate. The disease incidence rate is defined as the corresponding incidence rate per 1,000 population.

A linear model for predicting the malaria incidence using gender, age group, year, and sub-district as predictive factors gives a very poor fit, as shown by the Q-Q plots of the studentised residuals. This is because malaria incidence has a highly right-skewed distribution. But when we fit the same linear model to logarithms of incidence rates, the model fits very well, and the R^2 has almost doubled to 62.8% (Fig. 3). This is the ability of the model to predict incidence rate per 1,000 population.

A logistic model for predicting the malaria occurrence using gender-age group, year, sub-district, and population as predictive factors was assessed using ROC curve. The ROC curve shows how well a model predicts a binary outcome. It plots sensitivity (probability of finding an outcome when it is there) against the false positive error rate (probability of finding an outcome when it is not there). The cut-off point marked by the dot gives a total predicted number agreement of the number of cells in the model. The ROC curve shows that a model containing gender-age group, year, and sub-district as well as cell population fits the occurrence data very well. The model has an AUC of 0.8523 (Fig. 4), and it gives 91.79% predictive accuracy (number of correct predictions divided by the total number of all predictions).

Confidence intervals of malaria occurrence for levels of each predictive factor, including cell population from the logistic regression model, were plotted, with an overall mean of 10.9% (Fig. 5). Age patterns are different to those seen for incidence, with a peak at age 20–29 for males, a broader lower peak for females, and a decrease with age for each sex. Sub-districts show variation, with areas of high occurrence, especially in Yala. Thus, the disease is more likely to occur at these particular levels of predictive factors rather than at other levels.

The log-linear model's confidence intervals for the malaria incidence rate for each predictive factor were plotted (Fig. 6).The overall median incidence rate was 431 cases per 1,000 population, whereas the overall mean was 948 cases per 1,000 population. The larger value of the overall mean than the overall median is caused by a highly right-skewed distribution of malaria incidence rate. This does not affect the results from the model because the model was fitted to logarithms of incidence rates, which are normally distributed.

The incidence rate patterns show moderate increases with age for each sex, a decrease over the decade from 2008–2018, and high variation among sub-districts, with pockets of high incidence rate in Yala and Narathiwat.

A confidence interval plot of malaria incidence rate was used to divide sub-districts into three groups, depending on the placement of these intervals completely above, around, or below the overall median (Fig. 7B). The red color indicates sub-districts with incidence rate. Sub-districts with high malaria incidence are all located in the forested mountain range to the south-west. Most of these sub-districts were in Yala (all sub-districts of Than To and Kabang districts).

Similarly, a confidence interval plot of malaria occurrence was used to divide sub-districts into three groups depending on the placement of these intervals completely above, around, or below the overall mean (Fig. 7A). This map shows the pattern of malaria occurrence. We saw that the mountainous area bordering Malaysia is where malaria has high incidence rate, and it also has a high occurrence there. This map also shows that areas in the coastal plain of the Gulf of Thailand to the northeast have low to moderate malaria occurrences.

Table 1 summarizes the characteristics of malaria occurrence and incidence rate. Malaria occurrence was highest in 2008 (19.9%) and lowest in 2018 (4.6%), with the incidence rate appearing to be the same. The highest incidence was found in both males and females aged 20–29 years, with the incidence rate increasing with age in both sexes. The occurrence and incidence rates were highest in Yala province, while the lowest were in Songkhla province.

Table 1
Occurrence and incidence rate of malaria cases and social-demographic of malaria cases

Determinant	Occurrence (%)	Incidence rate/1,000 population
Year		
2008	19.9	6.90
2009	12.2	4.91
2010	12.6	5.65
2011	7.9	3.51
2012	9.1	4.33
2013	13.5	4.26
2014	12.4	4.08
2015	5.9	2.84
2016	13.9	4.40
2017	8.3	3.04
2018	4.6	2.34
Gender-age group		
Male		

Determinant	Occurrence (%)	Incidence rate/1,000 population
0–9 years	13.5	3.16
10–19 years	17.7	3.24
20–29 years	20.0	3.16
30–39 years	15.7	3.74
40–49 years	13.1	4.55
50–59 years	8.9	5.87
60–69 years	6.6	8.93
70 + years	3.6	9.35
Female	12.6	3.31
0–9 years	12.7	3.48
10–19 years	13.0	3.44
20–29 years	10.9	4.35
30–39 years	10.2	4.15
40–49 years	7.6	6.85
50–59 years	5.2	7.75
60–69 years	3.5	7.57
70 + years		
Province		
Yala	28.4	7.19
Pattani	5.0	3.24
Narathiwat	10.9	4.01
Songkha	7.6	2.55

A thematic map of all combinations of occurrence and incidence rate levels is shown in Fig. 8. Spearman's correlation coefficient between occurrence and incidence is 0.29. The area on this map where malaria occurrence and incidenc rate were both high very closely matches the area on the map of number of cases (Fig. 2) where all the sub-districts reported 25 or more cases over the 11 years.

Discussion

This work offered an approach to modeling incidence rates in cases when the Poisson and negative binomial distributions failed to fit the data. For such data, a logistic model for illness occurrence and a log-linear regression model for disease incidence rate were fitted independently. This approach provides a much better fit to these data and emphasizes the fact that the incidence rate increased with age for both sexes, whereas the occurrence rate peaked at young adult ages and subsequently declined with age for both sexes.

Our method of having separate models for occurrence and incidence rate provides a variety of benefits, especially when the predictors show different patterns. The occurrence patterns and incidence rate in our example differ by age. This method can be used to identify places with high malaria occurrence and incidence rates among susceptible persons, allowing health officials to take preventative actions to reduce the severity of impending epidemics. It can be used in a variety of other domains, such as ecology and environmental research, when data distributions are highly right-skewed and contain a large number of zeros. This method has the ability to depict malaria incidence on a finer spatial scale.

The incidence of malaria increased with age in both sexes. The only logical explanation for the increasing incidence with age is that the risk of infection increases as people age. For both sexes, the incidence peaked in early adulthood and subsequently diminished with age. This means that the agent must be presented in order for the sickness to manifest. Although the causes for the age difference between Plasmodium species remained unknown, it was indicated that it could be related to occupational exposure in older age groups of males. Naturally, mosquito-borne malaria infection occurs as a result of occupational exposures, notably for people working in community or social services, agriculture plantations, or forestry [24–25]. Additionally, it is due to risk behaviors, most notably those associated with inappropriate use of insecticide-treated nets or long-lasting insecticidal nets [26–28]. Another factor is defensive tactics or exposure to malaria control measures utilized in National Malaria Control Programs at the household level.

Between 2008 and 2018, there was a decline in incidence rates. This decrease was attributed to national policies for active management of foci, which included the full adoption of the 1-3-7 surveillance method for persistent active foci [29–30].

Malaria occurrence and incidence rates were both high in clusters of Yala province's sub-districts. This region, which shares a border with Malaysia, has been identified as a high-risk area for also other mosquito-borne diseases [31–33]. The available information in the literature for why this province had a high malaria incidence rate is lacking, however it may be because Yala has a large number of pocket sub-districts spatially related with malaria on the border. The Sankalakhiri Range is located between Yala and Perak on the Thai-Malaysia border[34]. Border malaria is complex in terms of both setting and dynamics, as a result of the links between human settlements and transportation activities [35]. Local border crossings and cross-border migration must be screened. Naturally, mosquito-borne malaria infection occurs as a result of risk behaviors, most notably those associated with improper use of insecticide-treated nets, long-lasting insecticidal nets, and other defensive measures, or those revealed by household-level implementation of malaria control measures recommended by National Malaria Control Programs

[28]. These major hotspot regions should be investigated in greater detail so that elimination activities can be targeted.

Although this study presents informative findings, it does have limitations. Spatial correlation in malaria incidence among neighboring sub-districts was not assessed by the proposed model. Further investigation is needed. Moreover, environmental characteristics of the sub-districts, for example, land use and land cover, are not included in the analysis. This aspect seems useful to explore in further studies.

Conclusion

Malaria incidence rates peaked in older age groups for both sexes, while the occurrence peaked in early adulthood for both sexes and clusters along the Thai-Malaysian border of Yala province. Malaria prevention and control efforts should be reinforced, with a particular focus on adults and communities living near forest fringes to keep track of progress toward the 2024 target of eradicating malaria. Thailand's Ministry of Public Health and Malaysia's Ministry of Health should cooperate.

Declarations

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2. Centre of Excellence in Mathematics, the Commission on Higher Education

***Conflicting Interest*:** The authors do not have any conflicts of interest to report.

Ethics approval and consent to participate

This study was approved from the Human Research Ethics Committee of the Prince of Songkla University, Pattani Campus. The approval number is psu.pn 1-007/63.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The first author planned the research, led the analysis and drafted the article. The second and third author planned the research, edited and contributed to the article, the fourth edited and led the data analysis.

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Figures

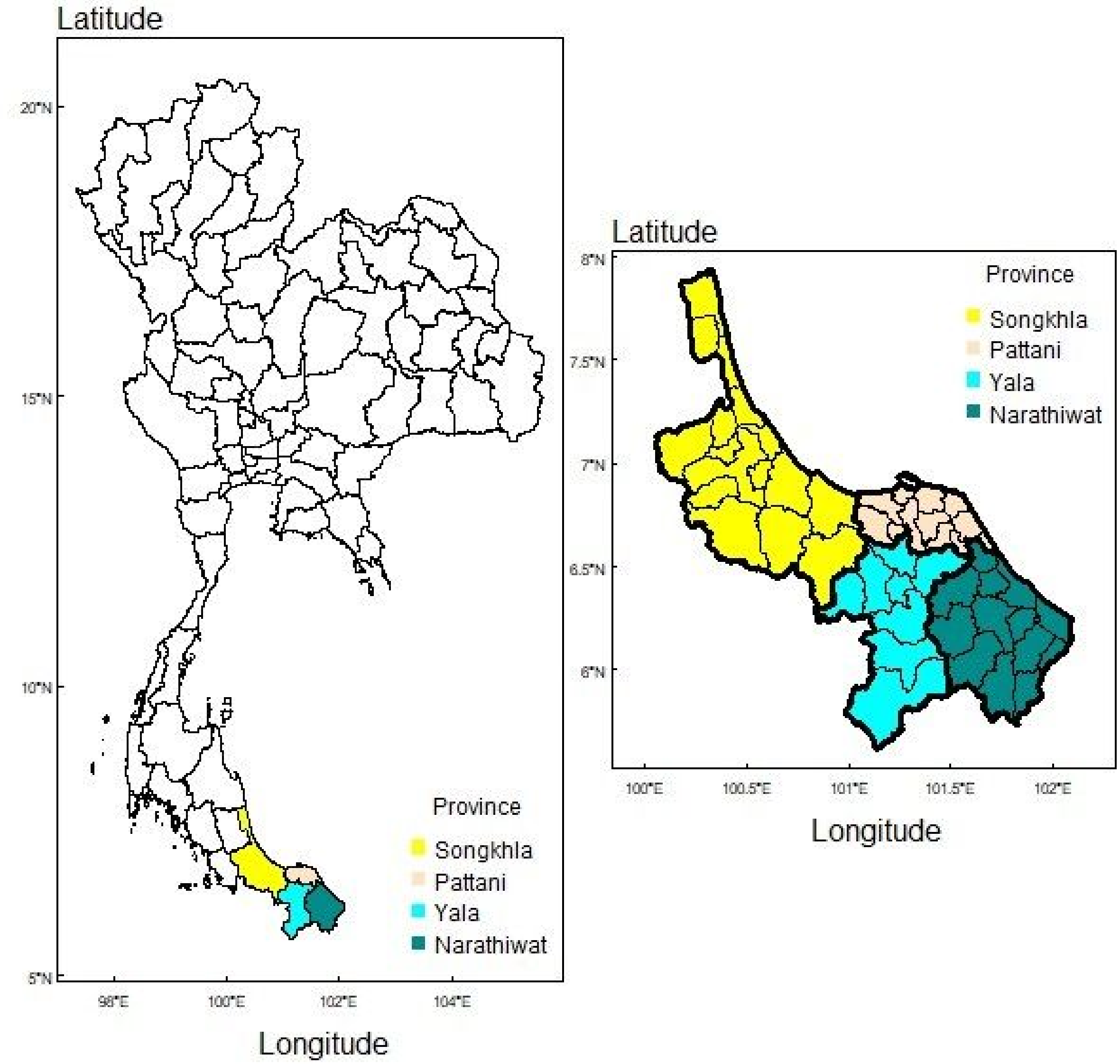

Figure 1

Study area comprises the four southernmost provinces of Thailand (Songkhla, Pattani, Yala, and Narathiwat)

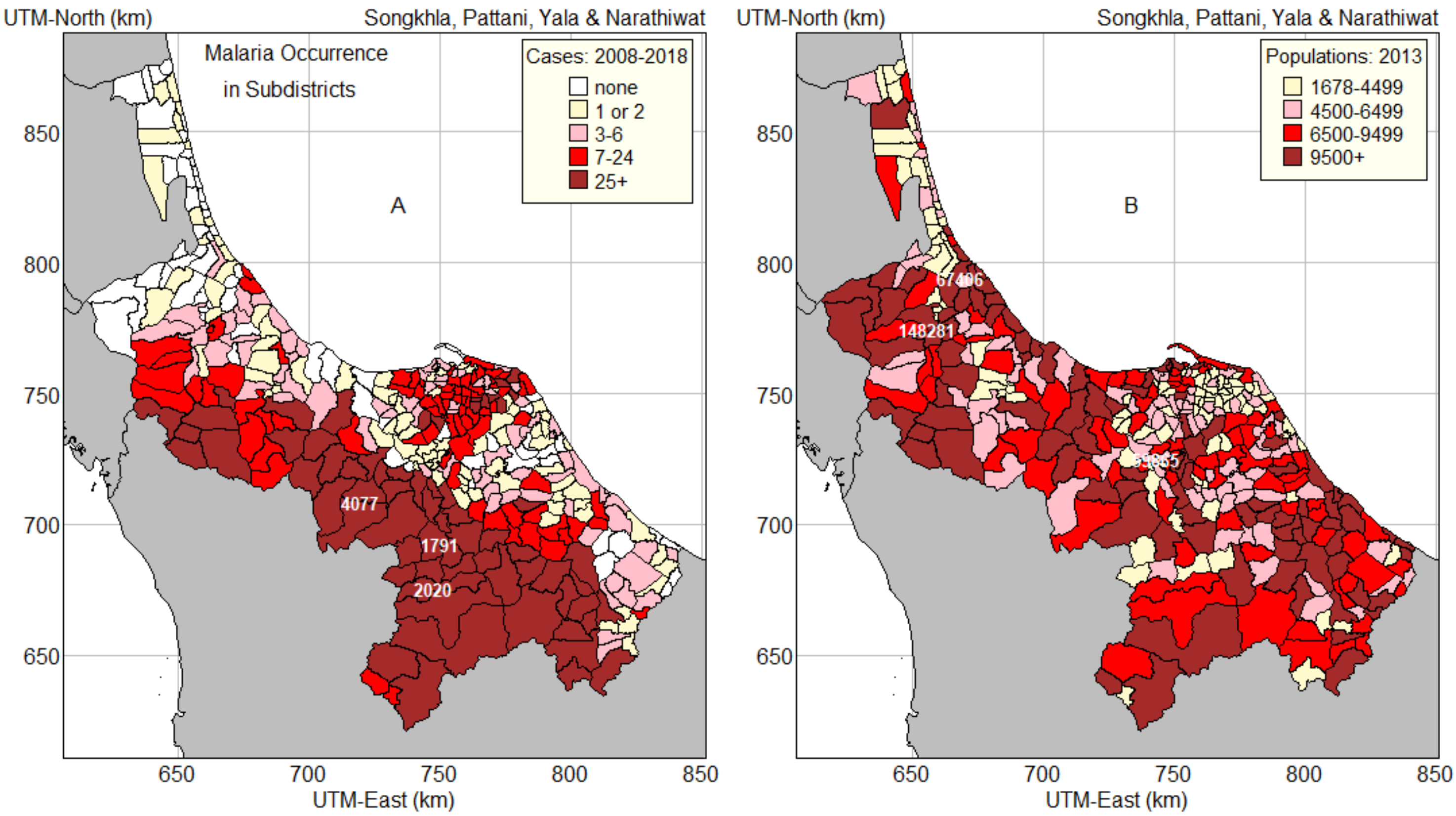

Figure 2

The number of malaria cases in 2008-2018 and the population count in 2013, shown by sub-district in the four southernmost provinces of Thailand

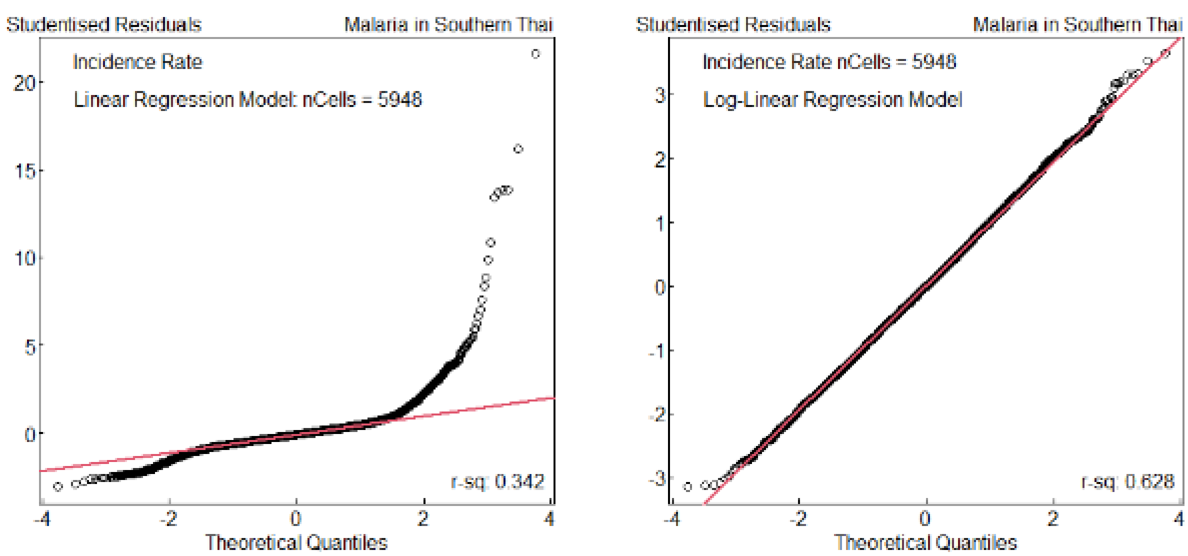

Figure 3

Quantile-quantile (Q-Q) plots of studentised residuals from linear and log-linear models

Figure 4

ROC curve for the logistic regression model

Figure 5

Malaria occurrence in 2008-2018 for levels of each predictive factor including cell population in four southernmost provinces of Thailand

Figure 6

Incidence rate of malaria in 2008-2018 for levels of each predictive factor in southernmost Thailand

Figure 7

Thematic maps of malaria occurrence and malaria incidence rate in 2008-2018 by sub-district in the four southernmost provinces of Thailand

Figure 8

Occurrence-incidence rate map of malaria in 2008-2018 in the four southernmost provinces of Thailand

Supplementary Files

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- Graphicalabstract.jpeg