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An ecological study of eosinophilic meningitis caused by the nematode, *Angiostrongylus cantonensis* (Chen, 1935) (Nematoda: Metastrongylidae)

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ABSTRACT

Climate change and other weather factors are associated with several infectious diseases, but are rarely reported as being associated with nematode infection. Eosinophilic meningitis (EOM) is an emerging disease worldwide caused by the nematode, *Angiostrongylus cantonensis*. It is transmitted through various agents such as snails and slugs. Temperature and rainfall are associated with snail population. There have been no previous studies on the relationship between weather and EOM. This was an ecological study. Numbers of EOM patients and weather data in Thailand's Loei province from 2006 to 2017 were obtained using a national database. A Spearman correlation was used to explore the relationship between EOM and weather variables. We developed a Poisson time series model combined with a distributed lag model (DLM) for estimating the effects of weather on EOM. We also created an autoregressive integrated moving average with exogeneous variable (ARIMAX) model for predicting future EOM cases over the following 12 months. There were 1126 EOM patients in the study. Among several weather factors, wind was significantly negatively correlated with the number of EOM patients (r_s: −0.204, 95% CI: −0.361 to −0.058; p value: 0.014). The ARIMAX(3, 0, 0) model with wind speed as a variable was appropriate for predicting the number of EOM patients. The predicted and actual numbers of EOM patients in 2018 were highly concordant. In conclusion, wind speed is significantly negatively correlated with the number of EOM patients.

1. Introduction

Eosinophilic meningitis (EOM), caused by *Angiostrongylus cantonensis* (Chen, 1935) (a type of nematode) is an emerging infectious disease worldwide [1]. Infected individuals suffer from acute severe headache that may last for almost two months [2]. Consumption of raw freshwater snails, shrimp, frog, or slugs is the main method of transmission to humans [3]. Thailand is the most endemic country for EOM. Of the 2827 reported cases of EOM in the literature from 1945 to 2008, 1337 (44.37%) were from Thailand (1). Outbreaks have also been reported in several other countries, mainly in the Pacific region [4–7].

Weather has been reported to be a predictor of outbreaks of various infectious diseases [8–10]. In Bangladesh, a possible association has been reported between temperatures of 33 °C and dengue in 16,030 patients by the end of this century [8]. Sea-surface temperature was related with 25% increases in the incidence rates of Cholera [10]. Moreover, climate or seasonal patterns are correlated with numbers of people affected by enteric bacterial diseases. For example, in northeast Vietnam, precipitation was significantly higher in high periods for Shigellosis than in low periods (236.7 vs 61.5 mm) [9].

As has previously been reported, climate change has affected the spread of various types of infectious diseases such as those that are vector borne or food borne. Numbers of Salmonellosis bacteria (a food-borne disease), for example, have been shown to increase in

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Table 1
Weather characteristics in Loei, Thailand from 2006 to 2017.

Variables, unit	Median	Range
Minimum pressure, hPa	1005.5	1001.1–1012.9
Average pressure, hPa	1008.9	1003.5–1016.4
Maximum pressure, hPa	1011.4	1005.2–1019.2
Minimum temperature, °C	22.4	11.9–24.7
Average temperature, °C	26.3	18.4–30.3
Maximum temperature, °C	32.2	26.1–39.6
Minimum humidity, %	59.4	36.2–75.8
Average humidity, %	81.2	59.6–91.2
Maximum humidity, %	96.0	83.4–98.8
Rainfall, mm	3.0	0–13.1
Evaporation, mm	3.3	2.5–6.3
Sunlight, hours	5.9	2.4–8.6
Wind speed, knots	1.2	0.2–2.0

temperatures between three and 37 degrees Celsius [11]. One way climate change may affect EOM is through its effect on the numbers of snails, slugs, or larvae. A study from India found that average minimum monthly temperature and average monthly rainfall were significantly correlated with future counts of giant African snails or *Achatina fulica* (Bowdich, 1822), an intermediate host of *A. cantonensis* (Chen, 1935), with correlation coefficients of 0.672 (p value < 0.05) and 0.820 (p value < 0.01), respectively [12]. However, there has yet been no report on the association between weather factors and occurrence of EOM. This study, thus, aimed to evaluate this association and develop a predictive model to aid in the forecast and control of future epidemics.

2. Materials and methods

This was an ecological study. We reviewed the annual EOM report from Thailand's National Disease Surveillance System from the Bureau of Epidemiology at the Ministry of Public Health's Department of

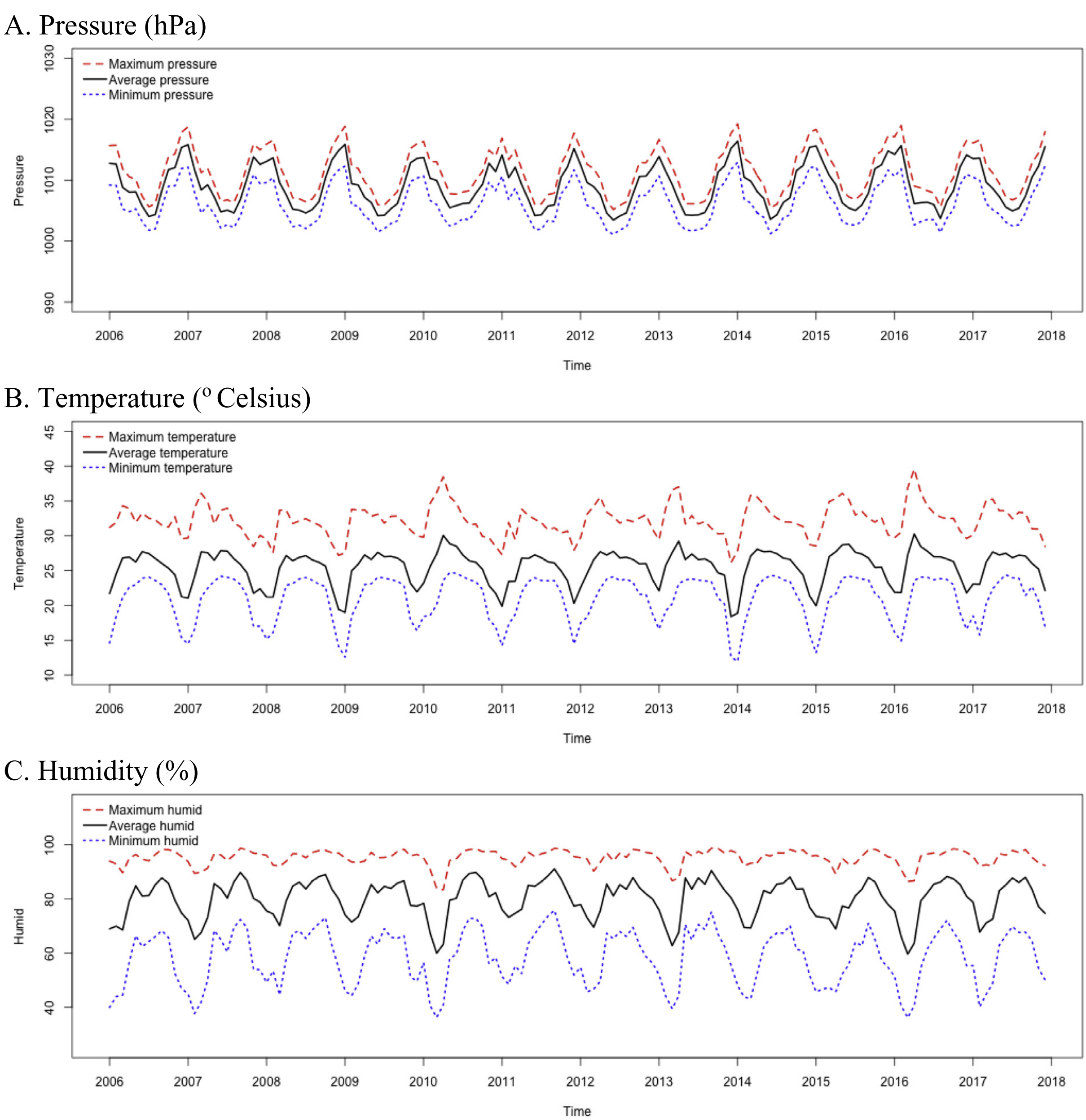

Fig. 1. Weather variables in Loei province between 2006 and 2017 including pressure (1A), temperature (1B), humidity (1C), rainfall (1D), Evaporation (1E), sunlight (1F) and wind speed (1G).

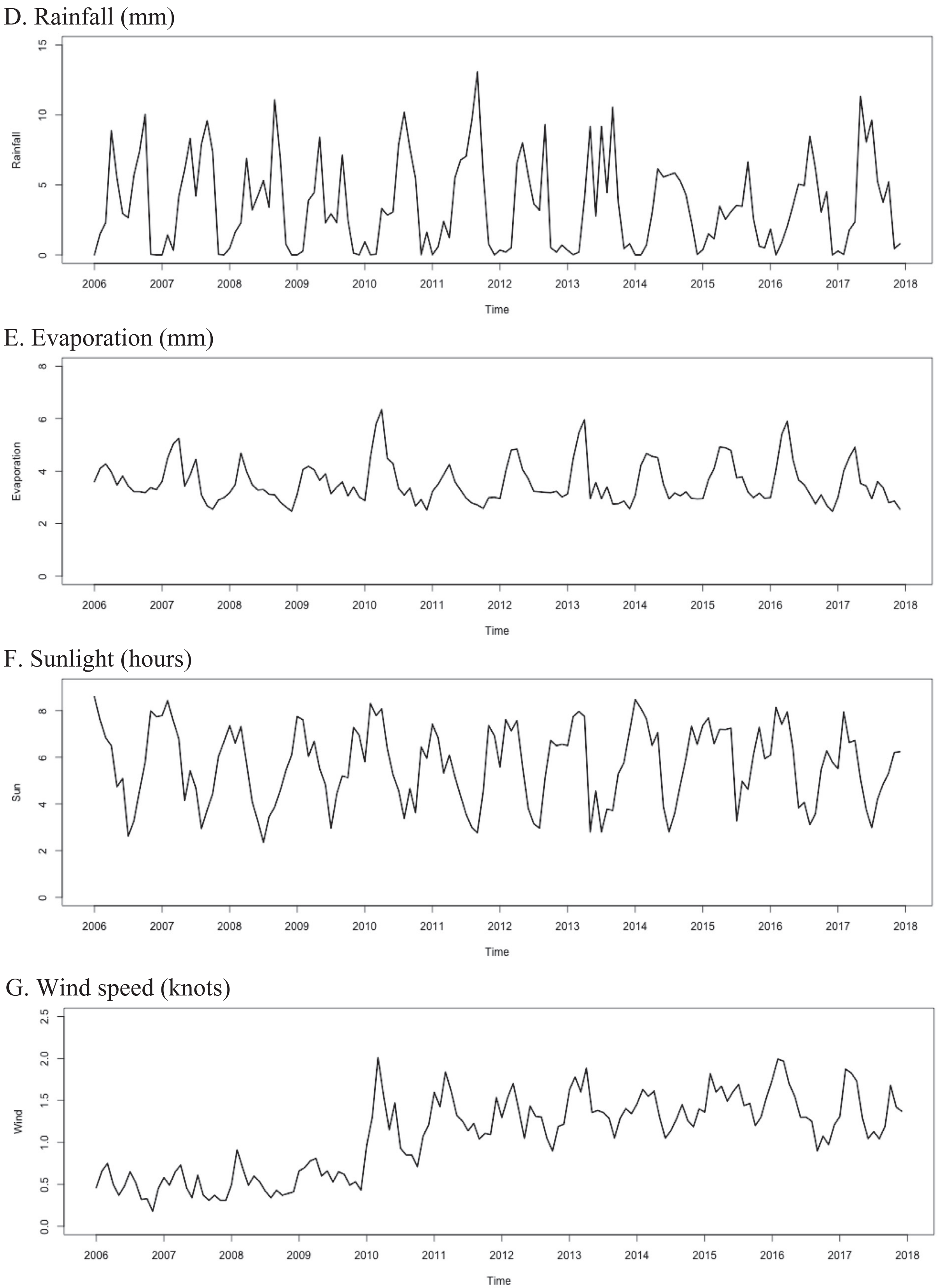

Fig. 1. (*continued*)

Table 2
Correlations between weather variables and number of eosinophilic meningitis cases by Spearman correlation.

Variables	Spearman correlation (r_s)			P-Value
	r_s	Lower 95% CI	Upper 95% CI	
Minimum pressure, hPa	0.061	−0.106	0.233	0.469
Average pressure, hPa	0.038	−0.130	0.201	0.653
Maximum pressure, hPa	0.023	−0.147	0.189	0.785
Minimum temperature, °C	0.012	−0.157	0.167	0.889
Average temperature, °C	−0.075	−0.230	0.091	0.374
Maximum temperature, °C	−0.094	−0.268	0.069	0.260
Minimum humidity, %	0.089	−0.091	0.247	0.289
Average humidity, %	0.103	−0.050	0.263	0.219
Maximum humidity, %	0.067	−0.094	0.211	0.423
Rainfall, mm	0.003	−0.170	0.175	0.970
Evaporation, mm	−0.154	−0.312	0.002	0.065
Sun, hours	−0.095	−0.255	0.073	0.255
Wind speed, knots	−0.204	−0.361	−0.058	0.014

Note. CI: confidence interval.

Table 4
An ARIMAX model for predicting future cases of eosinophilic meningitis in 2018 and actual numbers of cases in Loei, Thailand.

Months	Predicted number of cases	95% CI		Actual number of cases
		Lower	Upper	
Jan-2018	13.804	5.231	22.376	9
Feb-2018	12.874	3.962	21.786	10
Mar-2018	11.102	2.032	20.171	5
Apr-2018	10.937	1.648	20.226	6
May-2018	10.745	1.389	20.102	5
Jun-2018	10.091	0.701	19.481	11
Jul-2018	9.482	0.069	18.894	15
Aug-2018	9.546	0.124	18.969	21
Sep-2018	9.793	0.365	19.221	12
Oct-2018	9.669	0.238	19.099	14
Nov-2018	9.891	0.459	19.323	14
Dec-2018	9.300	−0.133	18.733	4
Total	127.233			126

Note. CI: confidence interval.

Disease Control (http://www.boe.moph.go.th/boedb/surdata/disease.php?dcontent=situation&ds=55). The system tracks reports of 52 communicable diseases, including EOM, from provincial public health offices, government hospitals, and public health centers throughout Thailand. The numbers of patients with EOM are reported by month and province.

Data regarding physical factors, such as pressure (hPa), temperature (°C), humidity (%), rainfall (mm), evaporation (mm), sun (hours), and wind speed (knots), were retrieved from the Thai Meteorological Department. All factors were reported as average values by month. Both numbers of EOM patients and data regarding physical factors were examined for Loei province, where EOM is the most endemic. The study period was between 2006 and 2017.

Statistical analyses. Medians and ranges were used to describe weather characteristics. A Spearman correlation was used to explore the relationship between EOM and weather variables with its 95% confidence interval (CI). A Poisson time series model combined with a distributed lag model (DLM) was developed for estimating the effects of weather on EOM. We defined delayed effects as a polynomial function. The maximum lag was four months and we used second order quadratic polynomial smoothing for the lag. Relative risk (RR) was plotted against related weather variables and lags. An ARIMAX model was created for predicting future EOM cases over the next 12 months.

During the modeling process, data was divided into two datasets (training and test). The training dataset consisted of data from January 2006 to December 2016, and was used to create the DLM and ARIMAX model. The test dataset consisted of data from January 2017 to December 2017 and was used to validate the models. The appropriate model was selected using a minimum Akaike information criterion (AIC) and a small root mean square error (RMSE) with a small number of exogenous variables. All statistical analyses were two-sided tests with a significant level of 0.05 and were conducted using R language [13] with "dlnm" [14], "forecast" [15], and "tseries" [16] packages.

3. Results

During study period, there were 1126 EOM cases in Loei province, with an average of 7.8 per month. The overall values of weather variables are shown in Table 1, while average values of weather variables by month during the study period are plotted in Fig. 1. The pressure was typically lowest in middle of each year (Fig. 1A). Temperature and humidity exhibited the same patterns, with lowest values being at the beginning and end of each year (Fig. 1B, C). Rainfall was highest in 2011 (Fig. 1D).

Table 3
ARIMAX model for predicting future cases of eosinophilic meningitis by weather variables.

Model	Fit		Predict
	RMSE	AIC	RMSE
1) ARIMAX(2, 0, 0) with average pressure, average temperature, average humidity, rainfall, evaporation, sunlight, and wind speed	4.101	769.341	0.192
2) ARIMAX(3, 0, 0) with average pressure, average temperature, average humidity, rainfall, evaporation, sunlight, and wind speed	4.074	767.706	0.033
3) ARIMAX(0, 0, 2) with average pressure, average temperature, average humidity, rainfall, evaporation, sunlight, and wind speed	4.198	773.537	0.496
4) ARIMAX(0, 0, 3) with average pressure, average temperature, average humidity, rainfall, evaporation, sunlight, and wind speed	4.071	769.429	0.291
5) ARIMAX(2, 0, 3) with average pressure, average temperature, average humidity, rainfall, evaporation, sunlight, and wind speed	3.928	769.120	0.114
6) ARIMAX(2, 1, 2) with average pressure, average temperature, average humidity, rainfall, evaporation, sunlight, and wind speed	4.231	775.283	1.29
7) ARIMAX(2, 1, 3) with average pressure, average temperature, average humidity, rainfall, evaporation, sunlight, and wind speed	4.059	770.131	1.458
8) ARIMAX(3, 0, 2) with average pressure, average temperature, average humidity, rainfall, evaporation, sunlight, and wind speed	4.023	770.452	0.096
9) ARIMAX(3, 1, 2) with average pressure, average temperature, average humidity, rainfall, evaporation, sunlight, and wind speed	4.043	768.355	1.437
10) ARIMAX(2, 0, 0) with wind speed	4.183	762.522	4.983
11) ARIMAX(3, 0, 0) with wind speed	4.128	761.146	4.975
12) ARIMAX(0, 0, 2) with wind speed	4.255	766.970	3.761
13) ARIMAX(0, 0, 3) with wind speed	4.138	761.745	3.711
14) ARIMAX(2, 0, 2) with wind speed	4.218	766.140	3.740
15) ARIMAX(2, 1, 2) with wind speed	4.226	766.628	3.401
16) ARIMAX(2, 1, 3) with wind speed	4.211	767.370	3.816
17) ARIMAX(3, 0, 2) with wind speed	4.082	762.324	3.438
18) ARIMAX(3, 1, 2) with wind speed	4.125	761.724	2.899

Note. RMSE: root-mean-square error; AIC: Akaike information criterion.

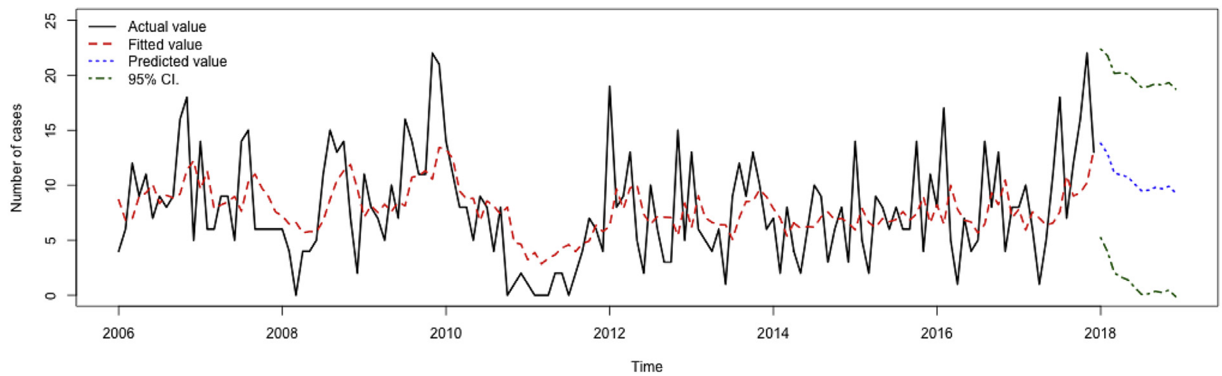

Fig. 2. An ARIMAX (3, 0, 0) model fitting with wind speed as a variable and numbers of eosinophilic meningitis (EOM) patients.
Note. CI: confidence interval.

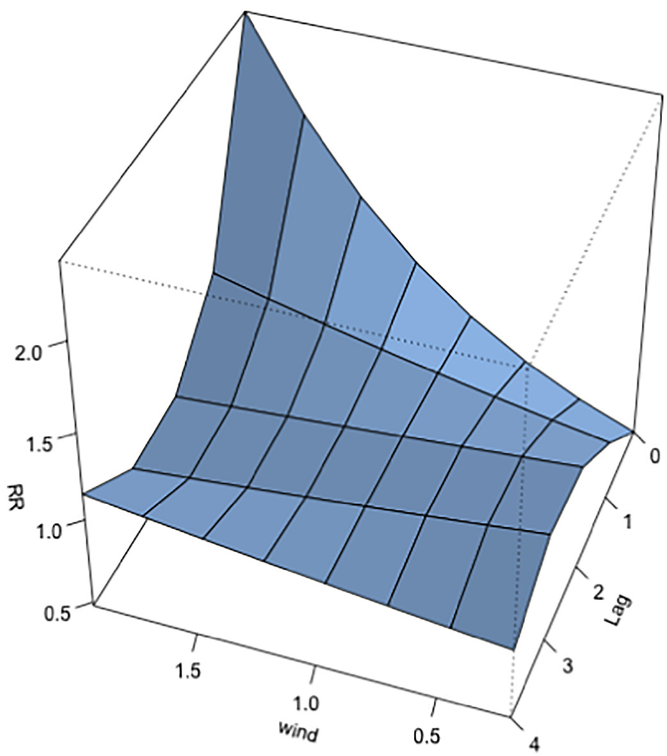

Fig. 3. Relationship between wind speed and eosinophilic meningitis at different lags.

The Spearman correlation found that only wind speed had a significant negative effect on the number of EOM cases with an r_s of −0.204 (95% CI: −0.361, −0.058; p value: 0.014), as shown in Table 2. We found that an ARIMAX (3, 0, 0) model that included wind speed as a variable was the best at forecasting future EOM cases due to its having the smallest AIC and there being only one covariate in the model (Table 3). The equation for the predictive model was as follows:

$$Y_t = 10.050 + 0.284Y_{t-1} + 0.115Y_{t-2} + 0.146Y_{t-3} - 1.983Wind_t$$

The number of EOM cases predicted for 2018 with 95% CI are presented in Table 4. The number of EOM cases was predicted to decrease slightly after January 2018 (Fig. 2). Only August had a higher number of patients than expected according to the 95% CI (Table 4). The total number of EOM patients in 2018 was identical with the predicted value at 128 patients (Table 4).

Fig. 3 is a three-dimensional plot that displays the association between wind and EOM at different lags. In the figure, we set wind equal to one as a referring value. We found the highest RR to be around 2.5 when the wind speed was close to two knots at lag 0.

4. Discussion

This present study showed that weather or climate had a significant effect on EOM caused by *A. cantonensis* (Chen, 1935). Wind was the only variable that had a significant negative correlation with EOM (r_s: −0.204; p value: 0.014). The negative correlation between wind speed and EOM may be explained by the effects of wind on slugs. *Limax maximus* (Linnaeus, 1758) is a type of slug that carries *A. cantonensis* (Chen, 1935) and serves as an intermediate host for the parasite [17]. Several studies have found that strong wind reduced both the number and activity of these slugs by between −0.12 to −0.23 and −0.05 to −0.09, respectively [18–21].

Strong wind may also affect aquatic or apple snails, rats, or even humans that may result in fewer numbers of EOM patients [22–24]. These phonomenons are explained by the following purposed mechanisms. A study from Florida showed that heavy wind made the snail kites unable to find the apple snails [25]. Similary, *Anastomus oscitansin* (Boddaert, 1783), an apple snail predator in tropical countries, is affected by wind as well. Nests of *Rattus rattus* (Linnaeus, 1758), a definitive host for *A. cantonensis* (Chen, 1935), may be destroyed by strong wind during the breeding season [26]. Farmers or local peoples in the northeast, Thailand are at risk for EOM due to habit of eating raw freshwater snails. The raw snail dish was flavoured with lime or local alcohol drink but it is still containing infective larva [24]. These people may have social meeting or party even if raining but not the strong wind conditions.

We also developed a wind model in this study. The 95% CI of predicted numbers of EOM patients included the numbers of EOM patients in 11 months of the following year. According to the data shown in Fig. 3, the highest relative risk for EOM was associated with the highest wind speed (two knots) and at the lag 0. These data may indicate that wind has the greatest effect on slug populations toward the beginning lag. Later on, the number of slugs may decrease with time [18]. Note that the number of EOM patients varied from month to month. There were more from June to November (Table 4) than in other periods. These high-prevalence months may be correlated with the months in which these snails reproduce (from June to September) [27]. The correlation between number of EOM patients and snail population may be due to weather or climate factors.

This study also had some limitations. As it was an ecological study, clinical factors were not included in the predictive model. In addition, this study may not be able to declare causal relationship between climate and EOM occurrence.

In conclusion, wind speed is negatively correlated with the number of EOM patients in a given area. The model we developed to predict EOM incidence, thus, includes wind speed as a factor.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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