Lagged effects of rainfall on malaria: a case study of Meghalaya

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Title: “Lagged effects of rainfall on malaria: a case study of Meghalaya”

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Abstract

Background: Meghalaya contributes about twenty per cent of India's total malaria death and is one of the high malaria endemic states in India, very susceptible to malaria transmission mainly due to favorable climatic conditions that mostly facilitate the transmission. In the relationship between malaria and meteorological factors, existing studies mainly focus on the interaction between different climatic factors, while interaction within one specific climatic predictor at different lag times has been largely neglected. This paper aims to explore the interaction of lagged rainfalls and their impact on malaria incidence.

Methods: The district monthly malaria records from Jan 2005 to December 2017 was collected from the Department of Health Services (Malaria), Government of Meghalaya. The district monthly meteorological records from Jan 2005 to December 2017 was collected from the Directorate of Agriculture, Government of Meghalaya, in which average temperature (°C), humidity (%) and rainfall (mm) had been recorded. Monthly malaria cases and three climatic variables of 4 districts in Meghalaya from 2005 to 2017 were analysed with the varying coefficient-distributed lag non-linear model. The missing climatic values were imputed using Kalman Smoothing on structural time series using the package *imputeTS* in R.

Results: During the period 2005-2017, a total of 309133 malaria cases were reported in all the districts under study. The monthly average rainfall ranges from a minimum of 181.79 mm in South Garo to a maximum of 367.87 in Jaintia. Also, South Garo and East Khasi are the hottest and the coolest place under study with 26.96 and 16.86 degrees Celsius respectively. Rainfall levels in the first-month lag affect the non-linear patterns between the incidence of malaria and rainfall at each lag time. The low rainfall level at the first-month lag may promote malaria

incidence as rainfall increases. However, for the high rainfall level at the first-month lag, malaria incidence decreases as rainfall increases.

Conclusion: The interaction effect between lagged rainfalls on malaria incidence was observed in this study, and highlights its importance for future studies to better understand and predict malaria transmission.

Keywords: Meghalaya, Malaria, Rainfall, Interaction, Distributed lag.

Background

Epidemiology describes malaria transmission in Meghalaya as perennial and persistent across the states and across the border with both *Plasmodium falciparum* and *Plasmodium vivax* found across the states (1). Meghalaya contributes about 20% of India's total malaria death (1) and is one of the high malaria endemic states in India, very susceptible to malaria transmission mainly due to favourable climatic conditions that mostly facilitate the transmission (2). The region received an average annual rainfall of over 2000 mm, and Cherrapunji, located on the Meghalaya plateau 50 Km south of Shillong, receives the highest rainfall in the world with a mean annual rainfall of 11,418.7 mm (3).

Apart from socio-economic conditions and agricultural practices, meteorological variables are the main drivers of malaria transmission (4) biologically speaking, weather conditions affect malaria incidence mainly through their effects on both the malaria vectors and the extrinsic incubation period of malaria parasites inside the mosquito vectors (5). The deposition of mosquito eggs and their maturation into larvae and then into adults required a suitable aquatic breeding site and is, therefore, dependent on rainfall and temperature. In cooler environments,

1 the increase in temperature shortens the parasite's life-cycle within the vector, enhancing
2 mosquito biting rate and thus increasing the transmission before the mosquito vector dies (6,7).

3 The existing relationship between meteorological variables and malaria failed to consider the
4 lag effect (4) but the issues of lag and the non-linear pattern are key when exploring the effect
5 of meteorological variables on malaria (5); for instance, a study in Meghalaya, observe a sudden
6 rise in malaria cases during May-July after the commencement of rainy season during April
7 but record low cases during Jan-April which corresponds to dry/low rainy season (1). On the
8 other hand, most time-series studies have established a relationship between meteorological
9 variables and malaria at a single fixed lag of 0, 1, or 2 months (6). However, the single lag
10 effect was not sensible enough to explain the relationship at a population level. The lag effect
11 was biologically divided into three stages, such as the development of mosquitoes from larvae
12 to adults, the extrinsic incubation period of parasites within the mosquito, and the incubation
13 of parasites within the human body (5). The extrinsic incubation period (EIP) describe as the
14 time it takes for the parasites to develop in the mosquito till the stage a mosquito becomes
15 infectious usually last on an average of 10 days and the development from larvae to the adult
16 stage usually last from 10 to 45 days. At each stage, the lag time may vary based on the changes
17 in climatic conditions. Evidence from existing studies suggests that lag and non-linear patterns
18 are essential, and a distributed lag non-linear model proves to be an appropriate method to
19 explore the effect of meteorological variables on malaria (8).

20 Existing studies on the relationship between meteorological variables and malaria primarily
21 focus on the lag effect and interaction between climatic factors (9) but the effect of between
22 lag interactions has long been neglected. Between lag interaction effect is defined as the
23 interaction between one covariate at a different lag time, for instance, the interaction effect of
24 rainfalls four and the five weeks previously on the malaria incidence of the current week,
25 whereas the interaction between various climatic factors are of the same time period and

simultaneously affect malaria incidence (10). This concept of interaction between lagged predictors was first used to examine the effect of heat exposure on excess mortality (11). This study investigates the interaction effect between several meteorological factors at different time lags on the risk of developing malaria. To our knowledge, this is the first study in the context of India. Particularly, using the monthly data on malaria cases and climatic variables during the period 2005-2017 in the districts of Meghalaya, a distributed lag non-linear model with varying coefficient was adopted to model the association between malaria cases and rainfall. The findings from the study will help to better understand the complex relationship between malaria transmission and climatic factors.

Methods

Study area

Meghalaya is one of the eight North-Eastern states of India bounded by Assam and Bangladesh and lies between $25^{\circ} 09' 30''$ N to $26^{\circ} 01' 42''$ N latitudes and $89^{\circ} 51' 25''$ E to $92^{\circ} 50' 37''$ E longitudes (Fig 1).

Geographically Meghalaya is divided into three hills (Khasi Hills, Garo Hills, Jaintia Hills) and politically into eleven districts. For this study, four regions comprised of four districts: East Khasi Hills, West Garo Hills, South Garo Hills, Jaintia Hills (West Jaintia and East Jaintia Hills) are taken. The remaining districts are not considered for the analysis due to a lack of information.

The climate of East Khasi Hills, in particular, is of interest to climatologists as Mawsynram and Cherrapunji, which are reported to be among the wettest places on the planet are located in this district. West Garo Hills and South Garo Hills being relatively lower in altitude, experiences a fairly high temperature for the most part of the year. Jaintia Hills formed a part

of the Meghalaya subtropical forests ecoregion and is considered one of the most species-rich areas of India.

Fig 1: Map showing the location of the study area.

Data source

The district monthly malaria records from Jan 2005 to December 2017 was collected from the Department of Health Services (Malaria), Government of Meghalaya. The district monthly meteorological records from Jan 2005 to December 2017 was collected from the Directorate of Agriculture, Government of Meghalaya in which average temperature (°C), humidity (%) and rainfall (mm) had been recorded. The administrative shapefile used to construct Fig 1 was obtained from GADM (<https://gadm.org/index.html>).

Distributed lag non-linear model (DLNM)

The non-linear and delayed dependencies can be described by a distributed lag non-linear model (DLNM) (8). A Poisson regression model was employed to model the expected number of malaria counts $E(M_{ij})$ in month j in district i and several climatic variables in previous months as,

$$\begin{aligned} \log(E(M_{ij})) = & \log(p_{ij}) + \beta_{i0} \\ & + \sum_{l=1}^6 f(x_{i(j-l),r}, \beta_{rl}) \\ & + \sum_{l=1}^4 f(x_{i(j-l),h}, \beta_{hl}) \\ & + \sum_{l=1}^4 f(x_{i(j-l),t}, \beta_{tl}), \end{aligned}$$

(1)

where M_{ij} and p_{ij} are the malaria counts and population in district i in month j respectively; β_{i0} is the intercept effect due to i^{th} district. $x_{ij,r}$, $x_{ij,h}$, $x_{ij,t}$ respectively represent the monthly rainfall, humidity and mean temperature in j^{th} month in i^{th} district.

Biological knowledge suggests that malaria cases in a particular month can be affected by climatic variables several months earlier for the lag effect in the model and hence, Model (1) estimates the cumulative effects across the whole lag range rather than at a single fixed lag time. Therefore, considering occurrences of malaria cases in a relatively long period i.e. monthly the model considers the lag ranges from the first to sixth month for rainfall and first to fourth month each for humidity and temperature. The model captures three key aspects - non-linear and lagged dependencies of malaria occurrence on meteorological variables, and the effect of between-lag interaction of rainfall on malaria occurrence (10). For the former, two basic functions are included in the model. The first basis function describes the non-linear effect of the meteorological variables that happened l months before the indexed month. The second basis function constrains the β s (β_{rl} , β_{hl} , β_{tl}) which accounts for the high collinearity caused by the significant correlation between the meteorological variables on consecutive months. The noise in the unconstrained distributed lag model can be reduced with less bias by the introduction of the constraining function (12). To investigate both basis functions in Model (1) a second-order natural cubic spline was applied in order to take into account the unimodal nature of climatic variables and parsimony of the model fitted (13).

To deal with the confounding effects induced by unmeasured district-specific variables the intercept term β_{i0} in Model (1) is modelled as a multilevel random intercept model following a normal distribution, $\beta_{i0} \sim N(\beta_0, \delta_0^2)$, β_0 is the mean intercept across all districts and δ_0^2 is the variability of district-specific intercepts around β_0 .

Distributed non-linear model with varying co-efficient

Model (1) is modified to include the lag interaction i.e. dependence of rainfall in month j on the level of rainfall in month $j-k$ in the form of a varying co-efficient distributed non-linear model (14). The rainfall in the first month is treated as the stratification variable in the study. To model the between-lag interaction of rainfall, all rainfall in one month lag i.e. $x_{i(j-1),r}$ were divided into three quantile groups (33.3 and 66.6% percentiles). The three groups were denoted as $R_{i(j-1,r0)}$, $R_{i(j-1,r1)}$, $R_{i(j-1,r2)}$ which represents the $x_{i(j-1),r}$ at the low, medium and high level of rainfall at the first-month lag, respectively. The modified version of Model (1) with those changes are as shown below,

$$\begin{aligned} \log(E(M_{ij})) = & \log(p_{ij}) + \beta_{i0} + \sum_{g=1}^2 \alpha_g X R_{i(j-1),rg} \\ & + \sum_{l=1}^6 f(x_{i(j-l),r}, \beta_{rl}(R_{i(j-1),rg})) \\ & + \sum_{l=1}^4 f(x_{i(j-l),h}, \beta_{hl}) \\ & + \sum_{l=1}^4 f(x_{i(j-l),t}, \beta_{tl}), \end{aligned} \quad (2)$$

$\beta_{rl}(R_{i(j-1),rg})$ indicates that the coefficient β_{rl} is now varying over $R_{i(j-1),rg}$, that is different levels of rainfall. Consequently, the effect of rainfall at other lag months is now dependent on the relevant rainfall level in the first-month lag. All the analysis was performed in the statistical software *R* and parameter estimation was done in the package *lme4* (15,16).

Results

Descriptive analysis

The missing climatic values were imputed using Kalman Smoothing on structural time series using the package *imputeTS* in *R* (15,17). During the period 2005-2017, a total of 309133 malaria cases were reported in all the districts under study.

The monthly average rainfall ranges from a minimum of 181.79 mm in South Garo to a maximum of 367.87 in Jaintia. Also, South Garo and East Khasi are the hottest and the coolest place under study with 26.96 and 16.86 degrees Celsius, respectively. East Khasi is also the most humid region under study in terms of monthly average relative humidity (78.95%) (Table S1).

The three rainfall ranges in the first-month lag are (0.0, 32.9 mm), [32.9, 305.4 mm), and [305.4, 3946 mm) with respective sample sizes of 207, 207 and 206. These values are grouped into the corresponding levels. The meteorological variables between different levels of rainfall have been compared visually by box plots, Fig 2. Only the levels of rainfall in the first-month lag were positively correlated with rainfall, humidity and mean temperature. Hence, one month lag is chosen as a stratification variable for further analysis in the study.

Fig 2: Distributions of meteorological variables by three rainfall levels at the 1st month lag. The dark line in the middle of the boxes represent the median values; the 25th and 75th percentiles of the distribution are represented by the bottom and top portions of the boxes, respectively; whiskers represent 1.5 times the height of the box; the value of outlier cases is represented by dots.

Distributed lag non-linear model with varying co-efficient

The estimated lagged non-linear relationships between malaria incidence and rainfall are shown in Fig 3. The Y-axis represents the logarithmic value of the relative risk of malaria incidence in comparison to the reference value at rainfall 0 mm. The dashed lines indicate a

95% confidence interval of the estimated non-linear effects of malaria incidence (solid lines).

In the low level of rainfall in the first-month lag, rainfall helps in increasing the incidence of malaria. However, in the high level of rainfall in the first-month lag, there is a negative association between malaria incidence and rainfall. A distinctive difference can be seen in the non-linear patterns between rainfall and malaria incidence at each time lag across the three levels of rainfall. In the case of the medium level of rainfall, a slight increase in the logarithmic value of the relative risk of malaria at first reaching the maximum at approximately 1500 mm, then starts declining sharply. Furthermore, in the high level of rainfall, a positive correlation is observed in the range 0-500 mm between rainfall and malaria incidence. Afterwards, the correlation becomes negative. In the low rainfall level in the first-month lag, rainfall is positively associated with the malaria incidence, and there is a sharp increase in log RR with the increase in rainfall. The third-month lag has the greatest impact on the risk of malaria at the low and medium levels of rainfall whereas, the effect of the second-month lag is greater than that of the fourth-month lag.

At low-level rainfall at one month lag, the relative risk of malaria gradually increases and then decreases with an increase in rainfall in two, three and four-month lags. Compared to medium and high-level rainfall, the interaction effect is quite low for low rainfall at one month lag. This indicates a pronounced interaction effect in medium and high-level rainfall in the first-month lag. Particularly the relative risk of malaria increases with an increase in lagged rainfall during medium rainfall in the first-month lag.

Panel (J-L) in Fig 3 demonstrate differences among 2, 3, 4 months lag for each rainfall level in the first-month lag. In the figure, the dotted, long dashed and two dashed lines represent two, three, and four months lag respectively. In low-level rainfall, the effect of four-month lagged rainfall is more pronounced than the other two. With the increase in rainfall at the fourth-month lag, relative risk increases to a certain level and then declines. After some point, rainfall at

fourth-month lag becomes negatively associated with malaria as log RR takes a negative value and decreases sharply. In a medium level of rainfall, the difference is negligible. In high-level rainfall, the rate of increase of risk is low for the fourth-month lag in comparison to two and three-month lags.

Fig 3: The estimates represent the non-linear patterns between rainfall and malaria incidences along the exposure dimension. The logarithm of the relative risk ratio in relation to the reference rainfall 0.0 mm is along the Y-axis. The solid line is the estimated non-linear fit with dashed lines representing its 95% confidence interval. The solid lines in the top 3 rows show the scenarios for the 2nd month lag (panel A–C), the 3rd month lag (panel D–F) and the 4th month lag (panel G–I), while the fourth row shows the difference among the results at the 2nd, 3rd and 4th month lags (J–L). The first three panels in each column represent the specific rainfall level at the first-month lag. Specifically, the columns of (A, D, G, J), (B, E, H, K) and (C, F, I, L) are for the low, medium and high rainfall levels at the first-month lag, respectively. The range of the X-axis depends on the corresponding observed range of rainfall.

Fig 4 shows the estimated lagged non-linear relationship between rainfall and malaria incidence in the lag dimension. Y-axis represents the log value of the relative risk ratio in comparison to the reference value of 0 mm rainfall. The solid line is the estimated non-linear curve with dashed lines indicating its 95% confidence interval. Panel a, b, c shows correlation at low, medium and high levels of rainfall, respectively.

The results are presented with three rainfall values at 25, 50 and 75% percentiles of monthly rainfall from 2005 to 2017, which are 12.5 mm, 206.5 mm and 400.5 mm, respectively. The

three representative rainfall values are within the three rainfall level ranges of Low: (0.0, 32.9 mm), Median: (32.9, 305.4 mm), and High: (305.4, 3946 mm).

The distributed lag curve shows the distinctive upward trend in all 3 panels. When rainfall is at 206.5 mm, the corresponding distributed lag curve drop until reaching the lowest point in the third month, then starts going upwards throughout. When rainfall is at 12.5 mm and 400.5 mm, both curves show similar trends. It is evident that log RR increases with both rainfall values and lag and the increasing rate is much larger in medium and high rainfall as compared to low rainfall.

Fig 4: This is the Fig 4 title **The estimates are for the non-linear patterns between rainfall and malaria incidence in the lag dimension. The *Y-axis* represents the logarithm of the relative risk ratio in relation to the reference rainfall 0.0 mm. The *solid line* is the estimated non-linear fit, with *dashed lines* representing its 95% confidence interval. The *three panels* of a–c show the scenarios for the rainfall levels of 12.5, 206.5, and 400.5 mm, respectively.**

Discussion

This study explores the interaction effect between rainfall at a different lag time and malaria incidence. The results show that the rainfall at the first-month lag affects the association between malaria incidence and rainfall at the other lag months, indicating the interaction effect between lagged rainfalls on malaria. When the level of rainfall at the first-month lag is low, the malaria incidence increases along with the increase of rainfall, indicating that the increasing rainfall helps malaria transmission when the rainfall level is low at the first-month lag. However, excessive rainfall decreases the risk of malaria transmission when the rainfall level is high at the first-month lag, as can be visualized from Panel C, F, I of Fig 3. Rainfall leads to many small puddles which increases the number of mosquitos breeding sites and enhances

1 mosquito survival due to the increase of humidity. However, abundant rainfall possibly washed
2 away or destroyed the mosquito breeding sites, and consequently reducing the mosquito density
3 (18). Specifically, when the level of rainfall at first-month lag is low, abundant rainfall at month
4 t would relieve the effect of low rainfall, so the rainfall would offer more numbers of breeding
5 sites, which then increased the risk of malaria incidence. In contrast, when the level of rainfall
6 at the first-month lag is high, then excessive rainfall at the month t would intensify the effect
7 of excessive rainfall, resulting in mosquitos breeding sites being destroyed and fewer people
8 doing their outdoor activities (10).

9 Also, it is observed that the lagged effect of rainfall on the risk of malaria incidence was highest
10 in the third lag month, compared to the second and fourth lag months. This may be due to the
11 fact that the effect of rainfall occurring during the current month or too long before has a
12 negligible impact on malaria incidence.

13 It can be observed from Fig 4 that higher relative risk due to the heavier rainfall results in a
14 shorter lag of malaria incidence. In the medium level of rainfall at the first-month lag, rainfall
15 starts to be significantly correlated with the malaria incidence at the fifth-month lag and
16 throughout. However, in the low and high levels of rainfall at the first-month lag, the rainfall
17 significantly correlates with the malaria incidence from the second-month lag onwards.
18 Rainfall in the medium level of rainfall at first-month lag is associated with delayed malaria
19 incidence as compared with the high level of rainfall. The reason may be that rainfall could
20 provide suitable habitats for mosquitos to breed, which then shortens their life cycle and
21 increases the spread of malaria (10).

22 To describe the main effect of the rainfall levels at the first-month lag, the term α_1 and α_2 are
23 introduced. It is observed as in Fig 2, the baseline distribution of climatic factors are not
24 identical across the three groups of different rainfall level at the first-month lag. The average

effect of the rainfall among the three groups is expected to be different even under the same rainfall conditions at the first-month lag; α_1 and α_2 are therefore added as the average deviation so that the values of log RR would be zero for all groups at the reference rainfall, and hence comparison of variations for rainfall is possible.

Confounding factors such as the malaria control interventions implemented by the individual district level may interfere with the relationship between meteorological factors and the incidence of malaria. Thus, the district-specific random intercept model is the perfect model that allows fitting a regression model to meteorological factors with the unexplained variations among the district under study. The variance δ_0^2 of the district-specific random intercept β_{i0} represent the variation between the districts that are not explained by the climatic factors and the potential bias caused by the omission of other climatic factors can be handled efficiently by the random intercept model (19).

The study has some limitations. First, the meteorological data are from the designated stations and may not represent the specific district. Second, the study is based only on four districts of Meghalaya. However, this should not induce any significant bias result. Third, the study did not analyse the characteristics of *Plasmodium falciparum* and *Plasmodium vivax* separately different from some existing studies in other countries (20,21) due to low cases of malaria in either of the measures in some of the districts. This may lead to mistaken *vivax* relapses as new infections due to meteorological factors. The lag non-linear patterns for the two types of malaria may be different to some extent.

Conclusions

Climatic factors influence malaria incidence in a complex way. However, this study highlights the importance of the interaction effect of meteorological factors by including in the

investigation of malaria incidence, which gives better information in understanding and predicting malaria transmission.

List of Abbreviation

EIP- Extrinsic incubation period

DLNM- Distributed lag non-linear model

HSC- Holendro Singh Chungkham

SPM- Strong P Marbaniang

HG- Hritiz Gogoi

Declarations

Ethical approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the office of the Department of Health Services (Malaria), and the office of the Directorate of Agriculture, Government of Meghalaya on reasonable request.

Competing interest: The authors declare that they have no competing interests

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Author's contributions: HSC, SPM conceived the study, involved in the study design, data analysis, interpret the data, drafted the manuscript. HG drafted the manuscript. All authors approved and agreed on the submitted final manuscript.

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Figures

Figure 1

Map showing the location of the study area.

Figure 2

Distributions of meteorological variables by three rainfall levels at the 1st month lag. The dark line in the middle of the boxes represent the median values; the 25th and 75th percentiles of the distribution are represented by the bottom and top portions of the boxes, respectively; whiskers represent 1.5 times the height of the box; the value of outlier cases is represented by dots.

Figure 3

The estimates represent the non-linear patterns between rainfall and malaria incidences along the exposure dimension. The logarithm of the relative risk ratio in relation to the reference rainfall 0.0 mm is along the Y-axis. The solid line is the estimated non-linear fit with dashed lines representing its 95% confidence interval. The solid lines in the top 3 rows show the scenarios for the 2nd month lag (panel A–C), the 3rd month lag (panel D–F) and the 4th month lag (panel G–I), while the fourth row shows the

difference among the results at the 2nd, 3rd and 4th month lags (J–L). The first three panels in each column represent the specific rainfall level at the first-month lag. Specifically, the columns of (A, D, G, J), (B, E, H, K) and (C, F, I, L) are for the low, medium and high rainfall levels at the first-month lag, respectively. The range of the X-axis depends on the corresponding observed range of rainfall.

Figure 4

This is the Fig 4 title The estimates are for the non-linear patterns between rainfall and malaria incidence in the lag dimension. The *Y-axis* represents the logarithm of the relative risk ratio in relation to the reference rainfall 0.0 mm. The *solid line* is the estimated non-linear fit, with *dashed lines* representing its 95% confidence interval. The *three panels* of a–c show the scenarios for the rainfall levels of 12.5, 206.5, and 400.5 mm, respectively.

Supplementary Files

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