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Research Article

Present and Future Distribution Model using MaxEnt: A Risk Map for Dengue Haemorrhagic Fever based on *Aedes aegypti* Mosquitoes Distribution in Malang Region, East Java, Indonesia

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ABSTRACT

The prevalence of Dengue Haemorrhagic Fever (DHF), a disease prevalent in countries with tropical and sub-tropical climates, including Indonesia, has exhibited a notable increase over the past two decades. A study case of a region experiencing this surge is Malang Region, which situated in East Java. The transmission of DHF within individual human is facilitated by the existence of *Ae. aegypti*, which serves as one of the intermediate vector mosquitoes. MaxEnt modelling was employed to analyse the niche and distribution of *Ae. aegypti*. The results of this study demonstrated that the integration of environmental and anthropogenic variables in a combination model provided more comprehensive approach for comprehending the niche and distribution patterns of *Ae. aegypti* compared to relying only regarding a climatic model. Areas characterised by higher temperatures, high population density, and limited vegetation cover possess the inherent capacity to serve as suitable habitats for *Ae. aegypti*. According to the modelling results, the distribution of *Ae. aegypti* in Malang region currently encompasses approximately 14.5 % (545.5 km^2) of the total area. It is projected that this distribution can potentially expand to 15.5 % (568.9 km^2) by the year 2040. Several sub-districts, namely Klojen, Blimbing, Sukun, Lowokwaru, Kedungkandang, Pakisaji, and Kepanjen, have been classified as high-risk areas that require special concern. The combination model of environmental variables and anthropogenic variables provide more comprehensive approach to understand the niche and the distribution patterns of *Ae. aegypti* in Malang Region compared to relying solely on climate models.

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INTRODUCTION

Dengue Hemorrhagic Fever (DHF) is a tropical and subtropical disease that is receiving increased attention in several regions of the world, including Indonesia (Capinha et al. 2014; Kraemer et al. 2015). The disease is caused by four types of dengue arbovirus (DENV-1, -2, -3, and -4), the family Flaviridae, the genus flavivirus, with the mosquito species *Aedes* aegypti serving as one of several vectors for transmitting the virus to humans (Tuiskunen & Lundkvist 2013; Swaidatul et al. 2022). According to Harapan et al. (2019) and the Indonesia Ministry of Health (2017), dengue case reports have increased in various regions of Indonesia over the past 2 decades. Although the implementation of the dengue preventive program initially led to a decrease in the number of cases, few years later there was a subsequent increase in the number of cases. This phenomenon is evident from the data compiled by Sulistyawati (2020) and The Indonesia Ministry of Health (2020), which reveals a significant increase in the number of cases since 2000, with fluctuations occurring between 2007 and 2018. In 2020, the number of individuals affected by DHF in this region increase significantly, with over 1700 people being afflicted (East Java Provincial Health Service 2021).

The Indonesia Ministry of Health (2017) implemented multiple strategies to counteract the spread of the dengue virus. Since the 1980s, vector control has heavily relied on active community participation, employing strategies such as larvicide use, fogging, mosquito nets, the 3M ("*Menguras, Menutup, Mendaur ulang barang bekas*") Program, larvae monitoring officers, elimination of mosquito nests, and the more recent "*Gerakan 1 Rumah 1 Jumantik*" (this movement is carried out by selecting a family member at home to monitor for larvae and using social media to report regularly) (Sulistyawati 2020). Nevertheless, according to Harapan et al. (2019), these strategies have not yet proven to be successful in significantly and optimally decreasing the number of individuals affected by dengue in Indonesia. The Indonesia Ministry of Health (2021) states that one of the challenges in dengue virus control is the lack of technology, so a quality and sustainable information system is expected to prioritise resource distribution to the most vulnerable regions. Tolinggi and Dengo (2019) suggested that utilising spatial niche analysis could serve as empirical evidence that is crucial for targeted interventions and can be used for designing programs aimed at preventing and controlling DHF.

Vector mosquitoes, such as *Ae. aegypti*, exhibit niches which provide a crucial role in determining their distribution. These niches are influenced by various factors, including environmental conditions (Lozano-Fuentes et al. 2012) and anthropogenic factor (Obenauer et al. 2017). The interaction of both factors in relation to the distribution of vector mosquito populations involves significant importance, particularly due to the anthropophilic nature of *Ae. aegypti* (Gomes et al. 2005). According to their nature, unique anthropogenic profile within a specified area, including population density and poverty also remain as spreading factor (Obenauer et al. 2017). Hence, the explanation of mosquito niches is not restricted to climatic factors, as this oversimplifies the dynamics of mosquito niche (Eisen & Moore 2013).

Climate change is a contributing factor to the distribution dynamics of *Ae. aegypti* populations, as these insects, like other poikilothermic species, are influenced by changes in temperature (Upshur et al. 2019). The IPCC (2021) has documented that global temperatures have, on average, risen by 1.07 °C between the years 1850-1900 and 2011-2019, with a range of 0.8 °C to 1.3 °C. The average land temperature is significantly higher, measuring 1.59 °C, with a variation between 1.34 °C and 1.83 °C. In addition, there has been an increase in both the intensity and frequency of rainfall as a climate variable since the 1950s (Wan et al. 2014; Knutson & Zeng 2018). Nevertheless, temperature and rainfall fluctuations exhibit significant variation across different geographic regions (Liu & Allan 2013; Schurer et al. 2020; Susilawaty et al. 2021). Therefore, it is imperative to conduct adjusted modeling in order to obtain accurate and representative results. The Coupled Model Intercomparison Project (CMIP6) is a widely utilised Global Climate Model. It is currently utilized alongside Shared Socioeconomic Pathways (SSPs) to establish emission scenarios (Meinshausen et al. 2020).

A commonly employed method recent times is machine learning (Witten et al. 2016). MaxEnt (Maximum Entropy), has gained significant popularity since its introduction by Phillips et al. (2006) as a machine learning algorithm. MaxEnt is a common technique for utilising presence-only data. It is known for its capability to incorporate background data and spatial variables as a deliberate approach (Peterson et al. 2011). Furthermore, MaxEnt, a type of machine-learning algorithm, is considered an effective modelling technique due to its capacity to accurately represent intricate patterns of data (Elith et al. 2010). Several research studies (e.g., Kraemer et al. 2015; Santos & Meneses 2017; Dickens et al. 2018; Iwamura et al. 2020, etc.) have used geographical distribution or ecological niche modelling to explore *Ae. aegypti* as a disease vector on a worldwide scale. Sallam et al. (2017) asserted that the utilisation of the MaxEnt algorithm for modelling the *Aedes* genera can be considered a suitable technique.

Nevertheless, conducting a reassessment specifically in the Malang region area is important due to the potential discrepancies in modeling outcomes between global and regional scales (Hastie et al. 2009; Früh et al. 2018). The objective of this research was to generate a spatial model using MaxEnt algorithm to determine the potential niche and distribution of *Ae. aegypti* in the region of Malang region. In addtition, a future distribution model was conducted to project the potential distribution of *Ae. aegypti* in the coming decades.

MATERIALS AND METHODS

Study Area

Malang region is a metropolitan area situated in the province of East Java, Indonesia and predominantly characterized by its highland urban and suburban areas, with the exception of its southern part which is a lowland area. This region is adjacent by several mountains (e.g., Mt. Bromo-Tengger-Semeru on the south side, Mt. Arjuno-Welirang and Mt. Panderman-Kawi-Butak on the west side). This region covers a total area of 3882.44 km^2 and is consists of three distinct administrative regions: (i) Malang City (145.28 km^2; 5 sub-districts), (ii) Malang Regency (3534.86 km^2; 33 sub-districts), and (iii) Batu City (202.3 km^2; 3 sub-districts) in (Figure 1).

Analysis

The modeling process involves utilising the occurrence data of encounter *Ae. aegypti*. In this study, two distinct models were utilised: (1) utilizing merely an environmental model, and (2) integrating both environmental and anthropogenic variable into a combined model. In addition, we projected future models involving two climate change scenarios using the present distribution model that performed the best. Furthermore, resampling was performed on all predictor variables. Multicollinearity tests are particularly necessary when examining environmental variables.

Data

A total of 35 occurrence data of *Ae. aegypti* in the Malang region was obtained through the collection of primary and secondary data sources from literatures (Gama et al. 2013; Gama & Salsabila 2021). Primary data collection was conducted at the larval and imago stages, using a random selection of locations both indoors and outdoors. Both active and passive methods were used to obtain samples. The larval sample collection was conducted using the dipping method, whereas the imago specimens were collected using aspirators. The larvae are collected using the passive method called ovitrap, while the adult mosquitoes are collected using a UV mosquito trap. In order to validate the species of mosquitoes, we adhere to the identification guidelines provided by Becker et al. (2020). Each sampling location coordinate recorded using GPS Garmin 64s.

The predictor variables utilised in our study are associated with environmental factors, such as climate and topography, as well as population characteristics, including population density and poverty number. The climate variable data utilised in this study was acquired from the WorldClim v.2.1 dataset (~1 km^2) (Fick & Hijmans 2017). Additionally, the topography data was obtained from the Shuttle Radar Topography Mission (SRTM) dataset (Jarvis et al. 2008). Furthermore, we obtained the Normalized Difference Vegetation Index (NDVI) variables (~30 m^2) and tree canopy cover data for the year 2000 from composite datasets of Landsat cloud-free images (Hansen et al. 2013). The latest available anthropogenic data pertaining to population density and poverty was obtained from the BPS-Statistics Indonesia Batu Municipality (2022), BPS-Statistics Indonesia Malang Municipality (2023), and BPS-Statistics Indonesia Malang Regency (2021).

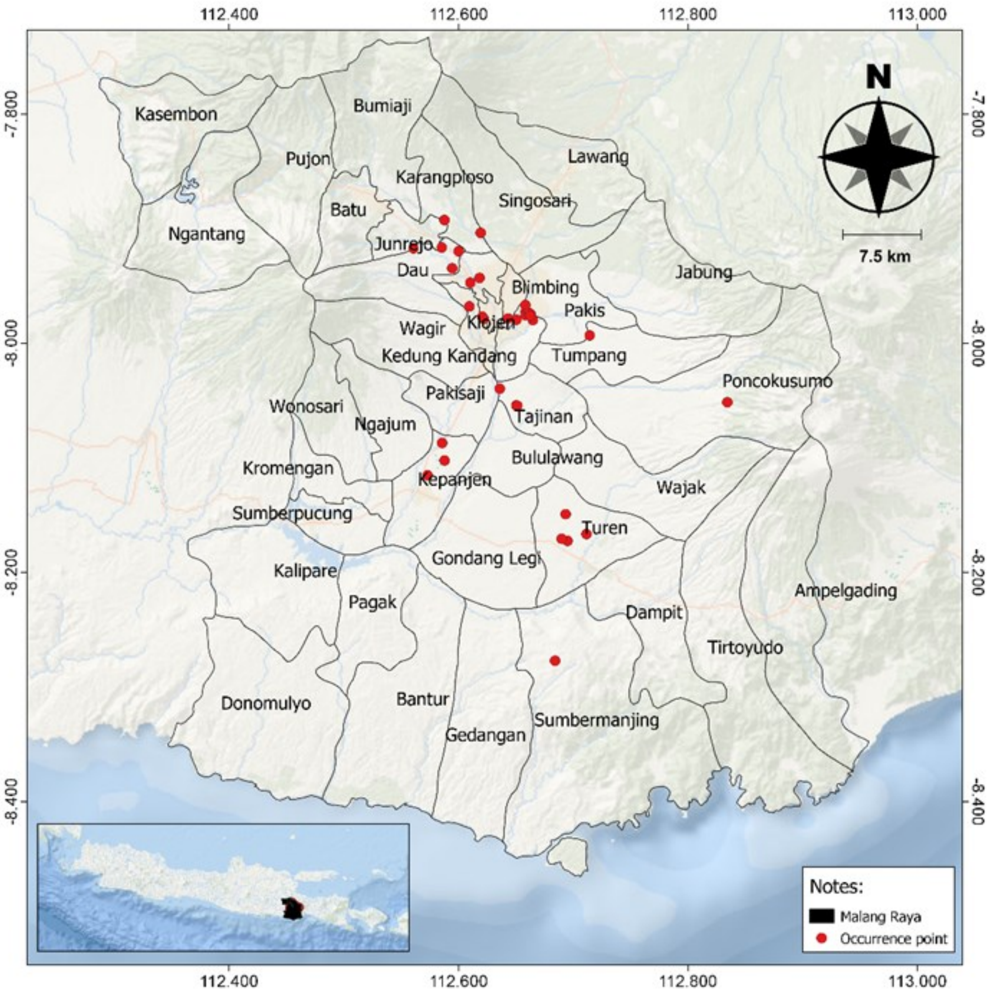

Figure 1. Occurrences of *Ae. aegypti* utilize in this study.

Preprocessing

The RStudio 2023.06.2+561 version software was utilised in order to carry out the preprocessing on each and every predictor variable. The raster representations of all environmental predictor variables are obtained, though not necessarily in the same resolution or spatial projection across the board. Hence, we are going to have to perform resampling using the raster package first (Hijmans 2023). We decided on a resolution of 250 by 250 meters so that it would be better to give the biological rational following Wiese et al. (2019). We determine variables related to the anthropogenic profile by referring to Obenauer et al. (2017), which are population density and poverty.

Variable selection

It is essential to evaluate the presence of multicollinearity among the predictor variables to prevent overfitting, which can render the model unsuitable (Pradhan & Setyawan 2021). A multicollinearity test was performed on all environmental variables utilising the VIF (variance inflation factor) statistical approach. The *vifcor* function, which is part of the *usdm* package (Naimi et al. 2014), is employed to perform this step. The VIF analysis generated results indicating that there were 10 environmental predictor variables that exhibited no issues of multicollinearity (Table 1).

Table 1. The variance inflation factor (VIF) values of the environmental variables selected in the modeling process.

Code	Variable	VIF value
bio2	Mean Diurnal Range	1.91
bio3	Isothermality	1.78
bio4	Temperature Seasonality	2.53
bio13	Precipitation of Wettest Month	14.48
bio14	Precipitation of Driest Month	23.72
bio15	Precipitation Seasonality	25.98
bio18	Precipitation of Warmest Quarter	6.45
Elev	Elevation	6.48
ndvi	Normalized Difference Vegetation Index Landsat 8	2.08
treecov	Tree Cover	2.22

Species Distribution Modelling using MaxEnt

Several distribution modelling algorithms have been employed to represent mosquito niches and spatial distribution, including the maximum entropy algorithm. The utilisation of this algorithm, which is based on machine learning, is widespread due to its ability to operate effectively with a modest quantity of presence data (Elith et al. 2006). The software utilised in this study was MaxEnt version 3.4.4 (Phillips et al. 2023), employing a cross-validated approach with 10 replications. A training presence threshold at the 10th percentile was employed, which involved excluding areas with habitat suitability values below 10 % of the encounter point. In order to enhance the optimisation of the conducted modelling, we implemented various adjustment in experimental parameters. These parameters include the q2lqpt threshold set to 0, the l2lq threshold set to 0, the beta threshold set to 1.83, the beta categorical set to 0.1, the beta lqp set to 0.9, and the beta hinge set to 0.5. It is essential to establish appropriate measures to reduce the possibility of overfitting or underfitting, particularly in scenarios where the sample size is relatively limited (Radosavljevic & Anderson 2014). In addition to the implemented modifications, the default adjustments provided by the MaxEnt software were utilised. The evaluation of the model generated in each iteration is conducted by evaluating the area under the curve (AUC) value revealed on the receiver operating characteristic (ROC) curve.

Data visualisation

We used QGIS 3.18 to visualize probability maps of *Ae. aegypti* distribution in each model, environmental and combination. After finding the model with the highest AUC value, which was assumed to be the best model, we mapped the area with the level of risk by adapting the HSC (Habitat Suitability Classification) classification concept carried out by Khan et al. (2022). HSC is categorised into five classes: p<0.2 (not suitable), 0.2-0.4 (least suitable), 0.4-0.6 (moderately suitable), 0.6-0.8 (highly suitable), and p>0.8 (very highly suitable). We also calculated the area of each class and made a ratio with the total area in each sub-district.

RESULTS

Environmental model

The Maxent model evaluation results indicated that a number of the selected environmental predictor variables (Table 1) comprised the most appropriate environmental model for estimating the presence of *Ae. aegypti* in the Malang region. The prediction reliability of the average value of the omission rate and predicted area was high. The replication resulted in an average AUC value of 0.877, with a standard deviation of 0.072. This value indicates that the predictive ability of the distribution modelling results is high.

According to the results of the jackknife analysis (Table 2), it is apparent that the variable with the highest percentage contribution was the mean diurnal range (bio2) variable. In addition, it was discovered that four additional variables exhibited a contribution percentage value exceeding 4 %. These variables include the normalised difference vegetation index (NDVI), isothermality (bio3), and tree canopy cover (treecov). Furthermore, the response curve is constructed as a probability estimation for a specific value of each variable (Figure 2). For instance, the variable bio2 exhibits an exponential increase within the temperature range of 7-10 °C, followed by a plateau once it surpasses 10 °C. Similarly, the variable NDVI demonstrates an exponential decrease within the range of 0-1, and then stabilizes after exceeding 1. Moreover, the variable bio3 displays an exponential increase within the range of 77-84, and then reaches a stagnation after surpassing 84. Furthermore, the variable treecov demonstrated a decreasing trend between 0-10 % and 50-100 %, while continuing to reach a stable state between 10-50 %.

Combination model (Environment + Anthropogenic)

The evaluation results of the MaxEnt model indicated that it exhibited robust predictive capabilities, as demonstrated by its performance when considering selected environmental predictor variables (refer to Table 1) in combination with population variables such as population density (PopDensity) and poverty (Poverty). The mean value of the omission rate and the predicted area demonstrated a high level of reliability in prediction. The mean area under the curve (AUC) value for the replication was found to be 0.890, accompanied by a standard deviation of 0.201. This finding suggests that incorporating both environmental and population variables in the modelling of *Ae. aegypti* distribution results in a more accurate and comprehensive model, as compared to utilising exclusively on environmental variables.

The findings of the jackknife analysis conducted on the combined variables (Table 3) regarding the relationship between environment and population exhibit that they congruent with the environmental model. This is evident as the variables bio2 (52.9 %) and ndvi (10.2 %) continue to demonstrate a substantial contribution percentage, despite the addition of the PopDensity variable (27.2 %) in the analysis. Despite the aforementioned, the response curve was generated to represent the probability estimation at specific values of each variable within the combination model (see Figure 3). Specifically, the variable "bio2" exhibited an increase within the temperature range of 7.0-10.25 °C, followed by a decrease beyond 10.25 °C. Similarly, the variable "PopDensity" demonstrated a decrease within the ranges of 0-500 and 2500-3500 families per subdistrict, while the probability increased within the range of 500-2500 household per subdistrict.

Table 2. Percentage contribution of environmental predictor variables based on jacknife analysis.

Predictor variable	Percentage contribution
bio2	63
ndvi	18.6
bio3	5.7
treecov	5.2
bio4	3.2
elev	1.4
bio13	1
bio14	0.9
bio18	0.9
bio15	0.1

Table 3. Percentage contribution of predictor variable involve in combination model based on jackknife analysis.

Predictor variable	Percentage contribution
bio2	52.9
PopDensity	27.2
ndvi	10.2
treecov	2.5
bio4	2.2
Poverty	2.1
bio3	1.5
bio13	0.6
elev	0.2
bio14	0.2
bio18	0.2
bio15	0.1

Future distribution model

Considering that a combination of models (based on AUC values) can precisely represent *Ae. aegyptis* niche and distribution, we tend to utilise this model to categorised risk level based on HSC (Habitat Suitability Classification). According to Figure 4, Malang City and several areas of Malang district have a high probability of encountering *Ae. aegypti*, while

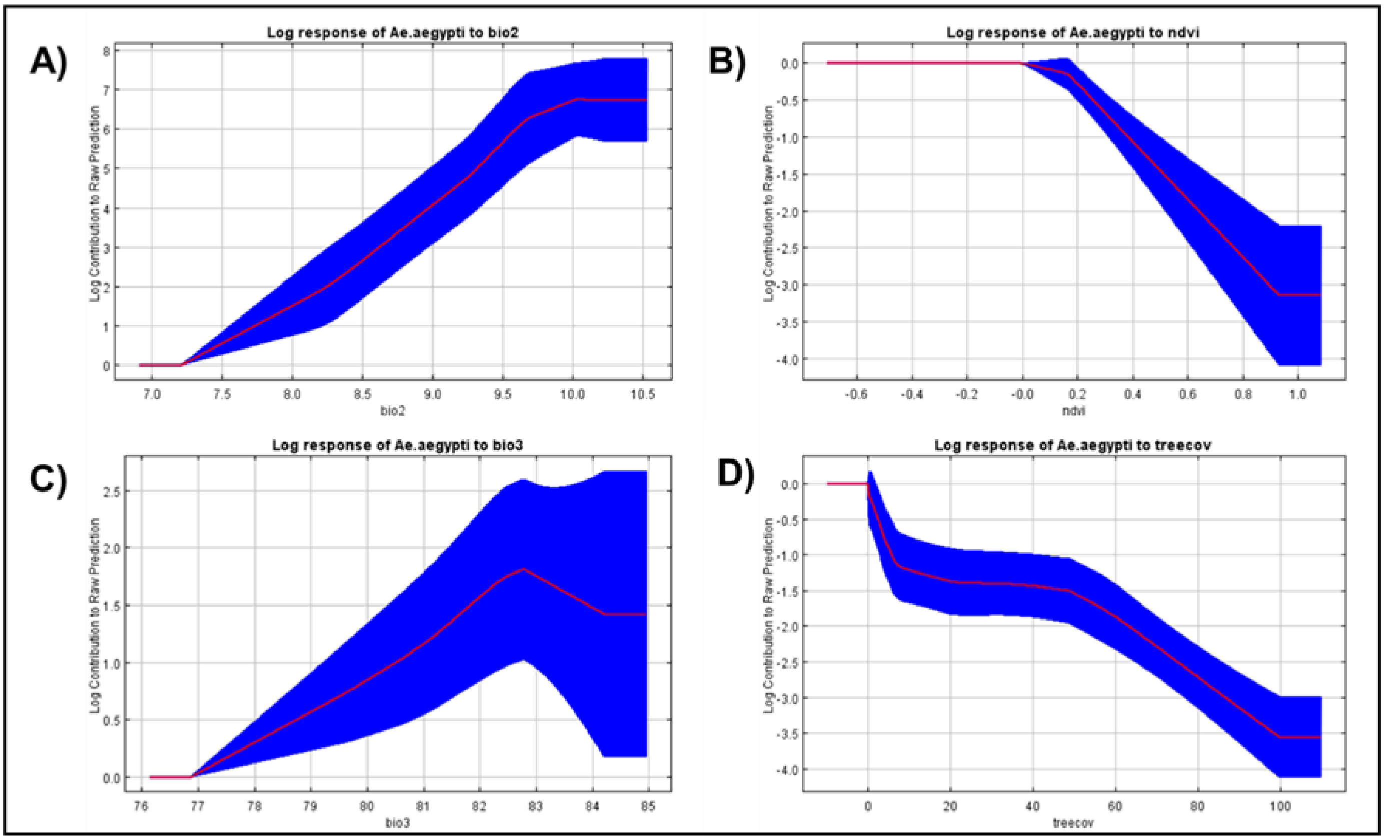

Figure 2. Variable response curve (contribution >4 %) according to environmental model.

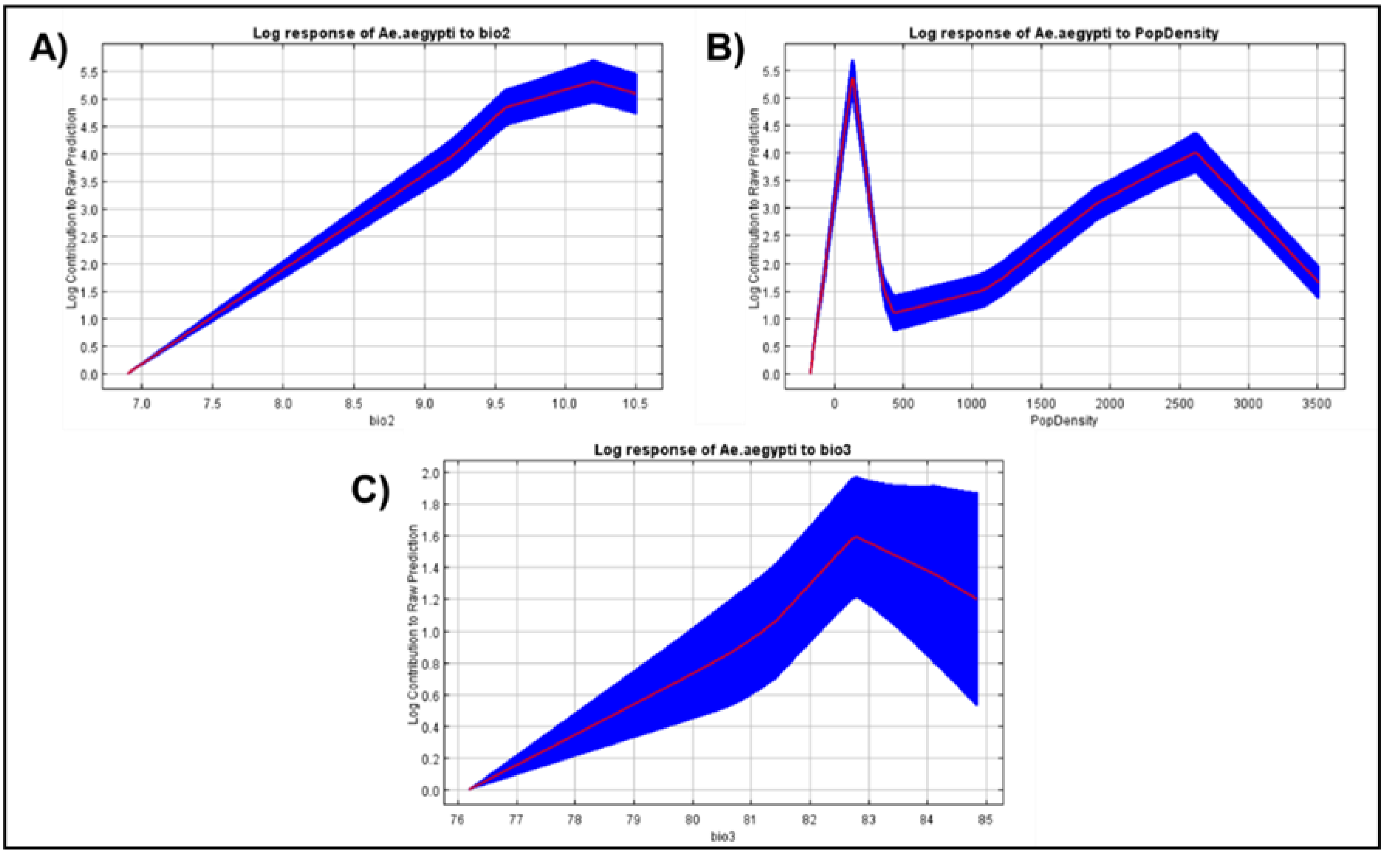

Figure 3. Variable response curve (contribution >4 %) in combination model (environment + population).

Batu City has a low probability. Malang Region has a potential distribution area for *Ae. aegypti* (HSC-2, HSC-3, HSC-4, and HSC-5) of approximately 545.5 km². The findings of our future projection analysis suggest a projected expansion in the suitable habitat for *Ae. aegypti* in 2040. The total area of this expansion encompasses a best-case scenario that involves an approximate expansion of 0.63 % (23.4 km²). In comparison, the worst-case scenario entails a 0.56 % expansion (21 km²) (Table 4).

The prioritisation of recommended locations for mosquito control in Malang Region is determined by calculating the ratio between the area in each HSC category and the total area in a sub-district. Several sub-districts within the Malang region exhibit the potential for dengue fever transmission, albeit occupying only 14.5 % of the total area. This likelihood is determined by the presence of areas with a probability exceeding 0.2, specifically within the HSC 2 to HSC 5 range. The districts in the Malang region that exhibit a habitat suitability percentage of over 50 % and highest HSC-5 ratio for the transmission of dengue fever in present distribution model, in sequential order, are as follows: Klojen, Blimbing, Sukun, Lowokwaru, Kedungkandang, and Pakisaji. In the projection of the *Ae. aegypti* distribution model for the year 2040, it is observed that several sub-districts continue to be classified as high-priority areas. The proportion of these sub-districts in the risk list is significantly greater when compared to the present distribution model. Furthermore, it has been observed that a specific sub-district, namely Kepanjen, which was previously excluded from the priority area, has indeed witnessed a rise in the proportion of suitable *Ae. aegypti* distribution (Figure 5).

Table 4. Current and future habitat suitability of *Ae. aegypti* in Malang region.

Habitat Suitability Classification	Current		2040			
			ssp126		ssp585	
	km²	%	km²	%	km²	%
HSC-1	3215.7	85.5	3194.3	84.9	3218.5	84.9
HSC-2	295.3	7.85	306.3	8.14	286.9	7.63
HSC-3	107.8	2.87	108.1	2.88	134.9	3.59
HSC-4	74.1	1.97	71.3	1.90	73.4	1.95
HSC-5	68.3	1.82	83.2	2.21	71.1	1.89
Total suitable area (HSC-2 – HSC-5)	545.5	14.50	568.9	15.13	566.5	15.06

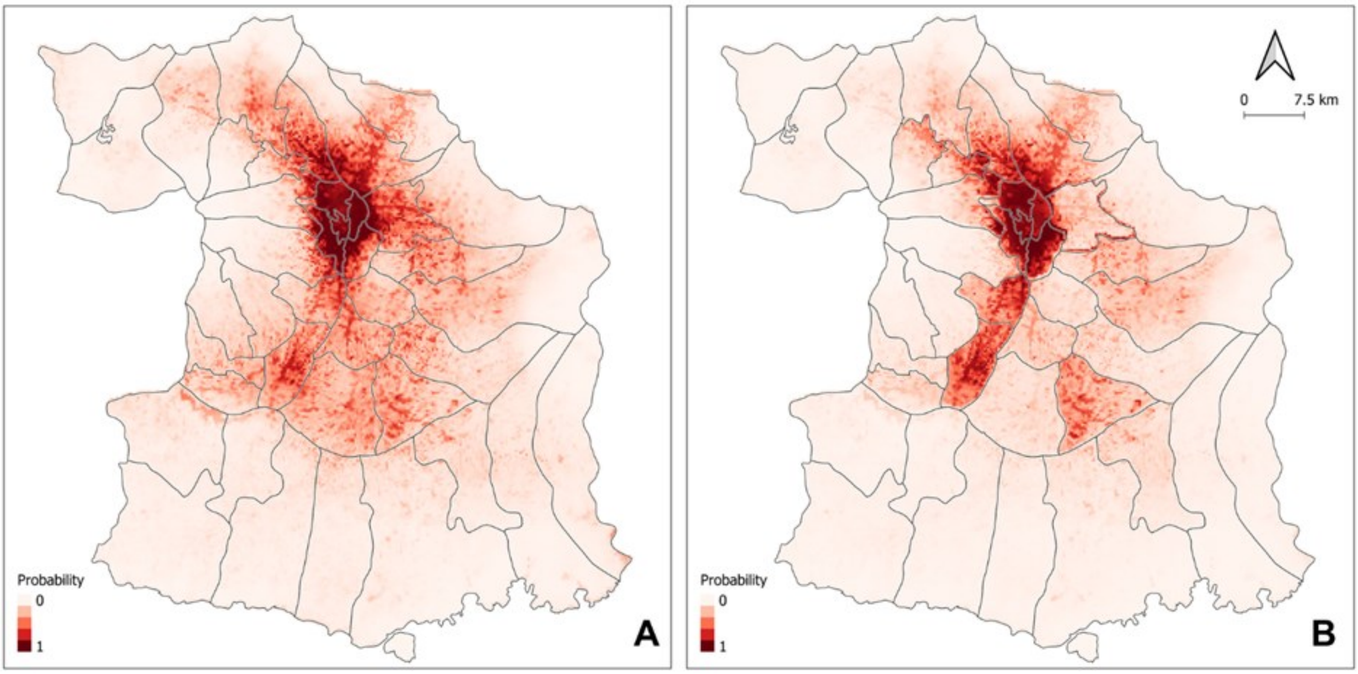

Figure 4. Possible extant of *Ae. aegypti* based on (A) environmental and (B) combination (environment + population) models.

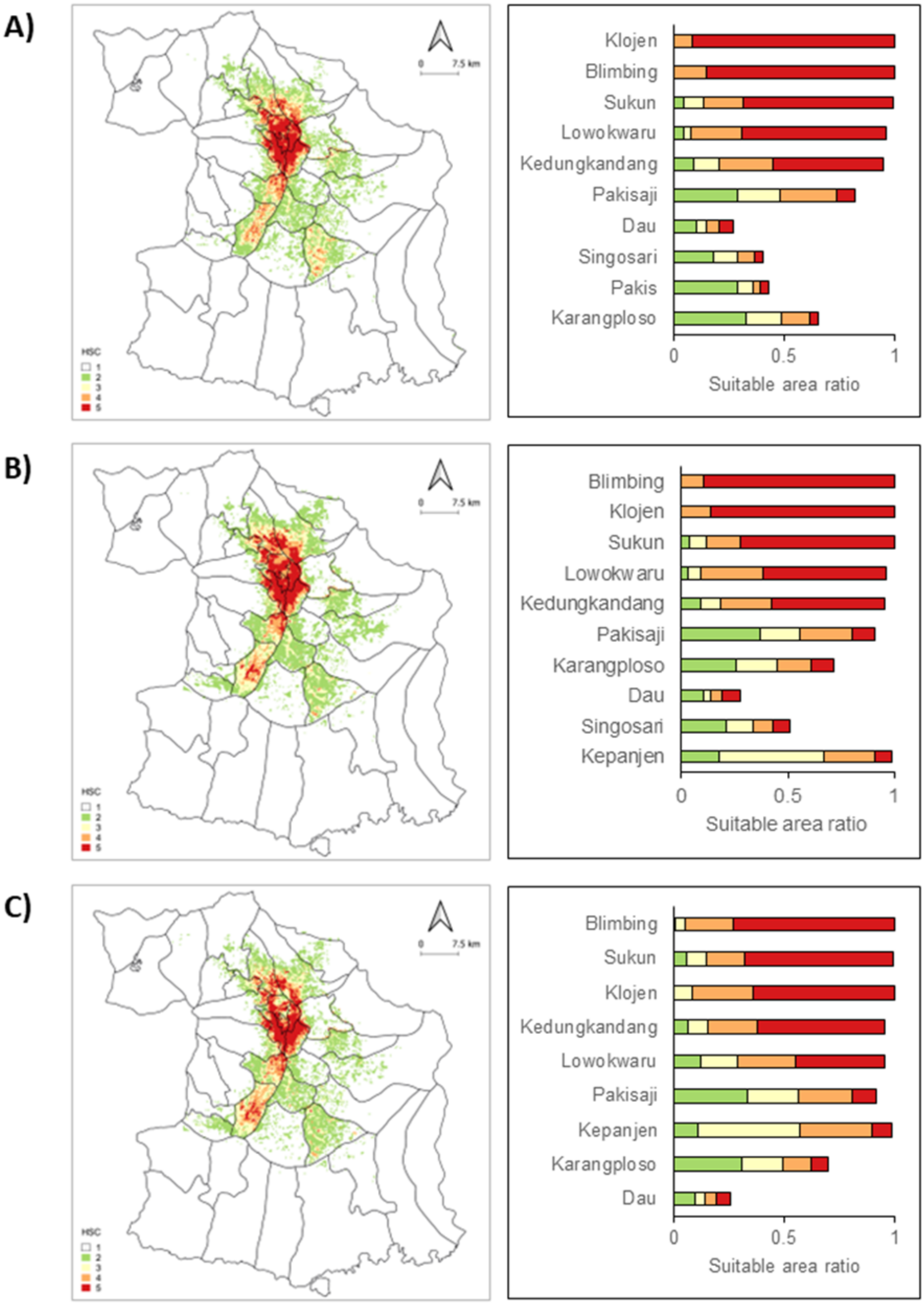

Figure 5. Spatial distribution of *Ae. aegypti* in each sub-district assessed based on HSC in (A) the present and the next 20 years ((B) best scenario and (C) worse scenario).

DISCUSSION

According to the outcomes of our modeling analysis, encompassing both environmental and combination models, it is evident that the prevalence of *Ae. aegypti* is notably higher in regions characterized by relatively warmer temperatures. Multiple prior studies have also reported similar findings (Lozano-Fuentes et al. 2012). The reason for this behavior can be attributed to *Ae. aegypti* poikilothermic nature (Upshur et al. 2019). Moreover, it is important to understand that elevated temperatures typically have an impact on the relative humidity as a result of evaporation phenomena (Thani et al. 2017). Consequently, under such circumstances, *Ae. aegypti* mosquitoes are able to fly without encountering any hindrance caused by the increased relative humidity present in the surrounding environment. Valdez et al. (2018) demonstrated that there exists a negative correlation between the abundance of *Ae. aegypti* and precipitation levels. The influence of climatic factors, such as temperature and precipitation, on mosquitoes or insects in general is well-recorded. However, it is noteworthy that vegetation conditions exhibit a distinct relationship with the habitat preferences of *Ae. aegypti*. Specifically, these mosquitoes tend to select areas characterized by low vegetation density.

Despite the fact that the environmental model demonstrates concordance with numerous studies and exhibits favourable model evaluation outcomes, the best model derived from this study was determined to be a combination of models integrating both environmental and anthropogenic variables. According to this model, it is hypothesized that, *Ae. aegypti* exhibits a preference for densely populated residential regions, with a particular preference for indoor habitats (Samson et al. 2015; Martin et al. 2019). This preference is associated with an attraction for human blood (Gomes et al. 2005; Mengko & Tuda 2016). Ratnasari et al. (2020) have also indicated that, *Ae. aegypti* commonly engages in oviposition within diverse categories of artificial receptacles that hold stagnant water, such as water drums, flowerpots, plastic cups, and discarded tires. Currently, the management of *Ae. aegypti* existence has proven to be challenging due to the diverse range of containers found in human settlements, which has led to uncertainty regarding their preferred sites for egg-laying (Hribar et al. 2004; Barrera et al. 2008; Arana-Guardia et al. 2014). The containers in question are frequently linked to disadvantaged areas of poverty (Obenauer et al. 2017; Martin et al. 2019; Souza et al. 2023). However, our model indicates that in the Malang region, poverty does not provide a significant contribution to our model. We hypothesise that, *Ae. aegypti* favours reproduction in various forms of standing water (Agustin et al. 2017), which is not exclusive to poor neighborhoods but can also occur in more affluent areas. Furthermore, urban areas that lack efficient waste management and drainage systems can serve as favourable environment for the development of *Ae. aegypti* mosquitoes (Banerjee et al. 2015), even though the socioeconomic condition of the subdistrict. Furthermore, the validity of the model's demonstration requires additional empirical research to verify the data in Malang region.

Our future projection model suggests that, *Ae. aegypti* may expand in 2040 within scenarios. In the best-case scenario, CO_2 emissions are reduced and dispersed more widely than in the worst-case scenario. This is unusual because insects prefer high CO_2 and temperatures (Menéndez et al. 2007; Menéndez 2007). The rise in temperature caused by CO_2 emissions may also contribute to this condition. High temperatures (20–30 °C) accelerate *Aedes* spp. metabolism, speeding up its life cycle. The rising temperatures in Malang region may lead to the spread of *Ae. aegypti*. In addition to in consequently, could result in an increase in reported cases of dengue virus, as indicated in previous research conducted by Stephenson et al. (2022). However, extreme high temperatures (>30 °C) directly affect the hatching percentage of *Ae. aegypti*, with higher temperatures resulting in fewer hatchlings and vice versa (Mohammed & Chadee 2011). *Aedes* spp. larvae and pupae develop in puddles of water, and relative humidity indirectly affects evaporation (Steinhoff et al. 2016). The presence of exceedingly elevated temperatures leads to a reduction in relative humidity and an increase in evaporation rates, thereby instigating competition among larvae. Increasing the evaporation rate reduces the standing water where *Aedes* spp. larvae develop, potentially reducing their density (Alto et al. 2015; Bara et al. 2015).

In general, the utilisation of MaxEnt as a distribution modeling method for the distribution of *Ae. aegypti* in the Malang Region demonstrates promising outcomes and can serve as initial data for subsequent investigations. Nevertheless, further investigation is required to validate the optimal ecological niche for *Ae. aegypti* and to effectively mitigate the transmission of DHF in Malang Region. This entails employing alternative algorithms (e.g., GLM or GAM), utilising predictor variables derived from locally accurate climate data. This research is particularly crucial in sub-districts with higher risk levels. In addition, it would be advantageous to acquire over time case data and involve direct observations to authenticate the congruity between the model constructed in this study and actual situations across different years.

CONCLUSIONS

The combination model of environmental variables and anthropogenic variables provide more comprehensive approach to understand the niche and distribution patterns of *Ae. aegypti* compared to relying solely on climate models. Areas with higher temperatures, high population densities, and limited vegetation cover could become suitable habitats for *Ae. aegypti*. Based on modeling results, the distribution of *Ae. aegypti* in Malang Region currently covers around 14.5 % (545.5 km^2) of the total area. It is projected that this distribution has the potential to expand to 15.5 % (568.9 km^2) in 2040. Several sub-districts, namely Klojen, Blimbing, Sukun, Lowokwaru, Kedungkandang, Pakisaji, and Kepanjen are classified as high-risk areas that require special concern.

AUTHOR CONTRIBUTION

Z.P.G., B.Y., and N.K. were responsible for the design of the study. M.F.A., M.A.R., and P.R both participated in the collection of data. Z.P.G., M.A.R., and R.J.K. participated in the analysis and interpretation of the data. M.A.R initially drafted the manuscript. Z.P.G., B.Y., and N.K. supervised the entire research project as well as reviewed, edited, also proofread the final draft.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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