Queensland University of Technology
Brisbane Australia

This may be the author's version of a work that was submitted/accepted for publication in the following source:

Dhewantara, Pandji Wibawa, Marina, Rina, Puspita, Tities, Ariati, Jusniar, Purwanto, Edy, Hananto, Miko, Hu, Wenbiao, & Soares Magalhaes, Ricardo
(2019)
Spatial and temporal variation of dengue incidence in the island of Bali, Indonesia: An ecological study.
*Travel Medicine and Infectious Disease*, *32*, Article number: 101437 1-10.

This file was downloaded from: https://eprints.qut.edu.au/131794/

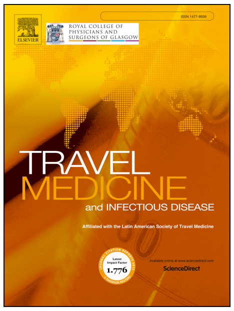
**© Consult author(s) regarding copyright matters**

This work is covered by copyright. Unless the document is being made available under a Creative Commons Licence, you must assume that re-use is limited to personal use and that permission from the copyright owner must be obtained for all other uses. If the document is available under a Creative Commons License (or other specified license) then refer to the Licence for details of permitted re-use. It is a condition of access that users recognise and abide by the legal requirements associated with these rights. If you believe that this work infringes copyright please provide details by email to qut.copyright@qut.edu.au

**License**: Creative Commons: Attribution-Noncommercial-No Derivative Works 4.0

**Notice**: *Please note that this document may not be the Version of Record (i.e. published version) of the work. Author manuscript versions (as Submitted for peer review or as Accepted for publication after peer review) can be identified by an absence of publisher branding and/or typeset appearance. If there is any doubt, please refer to the published source.*

*https://doi.org/10.1016/j.tmaid.2019.06.008*



# Spatial and temporal variation of dengue incidence in the island of bali, Indonesia: An ecological study

Pandji Wibawa Dhewantara, Rina Marina, Tities Puspita, Jusniar Ariati, Edy Purwanto, Miko Hananto, Wenbiao Hu, Ricardo J. Soares Magalhaes

PII: S1477-8939(18)30377-6
DOI: https://doi.org/10.1016/j.tmaid.2019.06.008
Reference: TMAID 1437

To appear in: *Travel Medicine and Infectious Disease*

Received Date: 16 November 2018
Revised Date: 27 May 2019
Accepted Date: 19 June 2019

Please cite this article as: Dhewantara PW, Marina R, Puspita T, Ariati J, Purwanto E, Hananto M, Hu W, Soares Magalhaes RJ, Spatial and temporal variation of dengue incidence in the island of bali, Indonesia: An ecological study, *Travel Medicine and Infectious Disease* (2019), doi: https://doi.org/10.1016/j.tmaid.2019.06.008.

# Spatial and temporal variation of dengue incidence in the island of Bali, Indonesia: an ecological study

**Pandji Wibawa Dhewantara**

Affiliation(s): Pangandaran Unit for Health Research and Development, National Institute of Health Research and Development (NIHRD), Ministry of Health of Indonesia, West Java 46396, Indonesia; UQ Spatial Epidemiology Laboratory, School of Veterinary Science, The University of Queensland, Gatton, QLD 4343, Australia

Email: p.dhewantara@uq.edu.au

**Rina Marina**

Affiliation: Center for Public Health Research and Development, National Institute of Health Research and Development (NIHRD), Ministry of Health of Indonesia, Jakarta 10560, Indonesia.

Email: rina.dhiowibowo@gmail.com

**Tities Puspita**

Affiliation: Center for Public Health Research and Development, National Institute of Health Research and Development (NIHRD), Ministry of Health of Indonesia, Jakarta 10560, Indonesia.

Email: tpuspita@gmail.com

**Jusniar Ariati**

Affiliation: Center for Public Health Research and Development, National Institute of Health Research and Development (NIHRD), Ministry of Health of Indonesia, Jakarta 10560, Indonesia.

Email: yusniarariati@yahoo.com

**Edy Purwanto**

Affiliation: Directorate for Surveillance and Health Quarantine, Directorate General for Disease Prevention and Control, Ministry of Health of Indonesia, Jakarta 10560, Indonesia. Email: edy.sukses.mulya@gmail.com

**Miko Hananto**

Affiliation: Center for Public Health Research and Development, National Institute of Health Research and Development (NIHRD), Ministry of Health of Indonesia, Jakarta 10560, Indonesia.

Email: hananto_miko@yahoo.co.id

**Wenbiao Hu**

Affiliation: School of Public Health and Social Work, Queensland University of Technology, Kelvin Grove, QLD 4059, Australia. Email: w2.hu@qut.edu.au

**Ricardo J. Soares Magalhaes**

Affiliations: UQ Spatial Epidemiology Laboratory, School of Veterinary Science, The University of Queensland, Gatton 4343 QLD, Australia; UQ Child Health Research Centre, Children's Health and Environment Program, The University of Queensland, South Brisbane 4101 QLD, Australia. Email: r.magalhaes@uq.edu.au

**Correspondence:**

Pandji Wibawa Dhewantara

Affiliation(s): Pangandaran Unit for Health Research and Development, National Institute of Health Research and Development (NIHRD), Ministry of Health of Indonesia, West Java 46396, Indonesia; UQ Spatial Epidemiology Laboratory, School of Veterinary Science, The University of Queensland, Gatton, QLD 4343, Australia

Email: p.dhewantara@uq.edu.au / p.dhewantara@gmail.com

## ABSTRACT

**Background:** Dengue fever control in the tropical island of Bali in Indonesia carries important significance both nationally and globally, as it is one of the most endemic islands in Indonesia and a worldwide popular travel destination**.** Despite its importance, the spatial and temporal heterogeneity in dengue risk and factors associated with its variation in risk across the island are not well understood. This study aimed to analyze for the first time the geographical and temporal pattern and the environmental and social drivers of dengue incidence in Bali.

**Methods: W**e analyzed retrospective dengue notification data at the sub-district level (*Kecamatan*) from January 2012 to December 2017 obtained from the Indonesian Ministry of Health. Seasonality in notified dengue incidence was assessed by seasonal trend decomposition analysis with Loess (STL) smoothing. Crude standardized morbidity rates (SMRs) of dengue were calculated. Moran's *I* and local indicators of spatial autocorrelation (LISA) analysis were employed to assess spatial clustering and high-risk areas over the period studied. Bayesian spatial and temporal conditional autoregressive (CAR) modeling was performed to quantify the effects of rainfall, temperature, elevation, and population density on the risk of dengue in Bali.

**Results:** Strong seasonality of dengue incidence was observed with most cases notified during January to May. Dengue rate was spatially clustered during the period studied with high-risk *kecamatans* concentrated in the south of the island, but since 2014, the high-risk areas expanded toward the eastern part of the island. The best-fitted CAR model showed increased dengue risk in *kecamatans* with high total annual rainfall (relative risk (RR): 1.16 for each 1-mm increase in rainfall; 95% Credible interval (CrI): 1.03-1.31) and high population density (RR: 7.90 per 1000 people/sq.km increase; 95% CrI: 3.01-20.40). The RR of dengue was decreased in *kecamatans* with higher elevation (RR: 0.73 for each 1-m increase in elevation; 95% CrI: 0.55-0.98). No significant association was observed between dengue RR and year except in 2014, where the dengue RR was significantly lower (RR: 0.53; 95% CrI: 0.30-0.92) than that in 2012.

**Conclusions:** Dengue incidence was strongly seasonal and spatially clustered in Bali. High-risk areas were spread from *kecamatans* in Badung and Denpasar toward Karangasem and Klungkung. The spatial heterogeneity of dengue risk across Bali was influenced by rainfall, elevation, and population density. Surveillance and targeted intervention strategies should be prioritized in the high-risk *kecamatans* identified in this study to control dengue transmission in this most touristic island in Indonesia. Local health authorities should recommend travelers to use personal protective measures, especially during the peak epidemic period, before visiting Bali.

**Keywords:** dengue, Bali, spatial analysis, conditional autoregression model, risk factors, travel medicine

## 1. Introduction

Dengue fever (DF) is an important mosquito-borne viral infectious disease that affects populations living in tropical and subtropical regions [1]. The infection is caused by four unique dengue virus strains (DENV-1 to DENV-4) belonging to the Flaviviridae family and are transmitted by *Aedes aegypti* and *Aedes albopictus* mosquito [2]. Annually, worldwide, approximately 390 million cases are reported and at least 2.5 billion people are at high risk, of which more than 70% population at risk are living in Southeast Asia and the Western Pacific Region [1]. International travel, climate change, and urbanization are claimed to drive the geographical spread of the disease from endemic regions throughout nonendemic regions, thus leading to increased risk and burden worldwide [3-6]. Furthermore, currently, there are no effective vaccines available for dengue [7, 8]. Vaccination has been trialed in many endemic Asian countries including Indonesia [9, 10]. Although these studies have demonstrated the potential benefit of vaccination, the potential adverse effects after vaccination remain concerning, which may increase the incidence of severe dengue cases in particular age groups, in areas with low prevalence, and among those individuals who have not previously been infected by dengue virus [11, 12].

Indonesia, the most populous archipelagic tropical country in Southeast Asia, is a dengue-endemic country where dengue transmission occurs continuously [13]. Dengue outbreak was first reported in Jakarta and Surabaya in 1968 [14]. Since then, the disease has been spreading among all provinces, and it continued to increase, reaching the highest reported incidence in 2010 (85.70 per 100,000 people). Dengue infection disproportionately affected children of age 5 to 14 years and adults of age more than 15 years [15]. To date, dengue outbreaks have been reported in all 34 provinces and 514 districts across the country, indicating that dengue remains a significant public health problem in the country. To reduce its burden, Indonesia health authority-implemented strategies focus on controlling the vector population through community-based vector-control action (e.g., reduction in breeding sites) as well as chemical-based control approaches (e.g., spraying larvicide and insecticide).

In Indonesia, Bali is one of the provinces with the highest dengue incidence [16]. All four dengue virus strains have been found to circulate in the island [17, 18], thereby emphasizing that Bali is an important spot for dengue circulation in the region [19-21]. This situation is particularly problematic, as the island of Bali is also a popular tourism destination in the Asia Pacific that attracts millions of international travelers annually. It is estimated that more than 4 million international tourists visit Bali each year [22], as well as millions of domestic visitors come from other dengue endemic islands of Indonesia. Recent studies have shown that Bali is one of the endemic sources of dengue infection among international travelers [23, 24]. Despite the high importance of dengue in Bali, the geographical variation, as well as factors driving it, such as spatial heterogeneity in the risk of dengue across the island, is far from clear. This information would be paramount to enhance current dengue control strategies to protect the local Balinese population as well as global travelers in this region.

Geographical information system (GIS) and remote sensing (RS) have currently been widely used in public health to help reveal the spatial epidemiology of diseases and improve surveillance systems for vector-borne diseases [25, 26]. Spatial analytical tools could help provide evidence to support intervention strategies including identifying high-risk areas and determining where resources should be allocated the most. In Indonesia, few studies have demonstrated both the value of GIS/RS technologies and spatial statistics in investigating the geographical and temporal pattern of diseases and predicting risks, especially for dengue infections [27-31]. To date, there have been no studies on the geographical and temporal pattern of dengue incidence and its associated drivers, especially in the island of Bali.

In this study, therefore, we aimed to analyze the spatial and temporal pattern of notified dengue incidence in Bali between 2012 and 2017 and to quantify the role of social and environmental factors in the spatial variability of dengue risk in Bali. This study was expected to provide evidence base to better inform local health authorities to identify high-risk areas as well as the drivers associated with variation in dengue risk in mainland Bali, so that cost-effective and targeted interventions could be strengthened.

## 2. Methods

### Study site

Bali is one of the 34 provinces of Indonesia and is located between Java and Lombok (-8.0611 to -8.8466 S and 114.4314 to 115.7111 E). Bali consists of the mainland and five small islands, namely, Nusa Penida, Nusa Ceningan, Nusa Lembongan, Serangan, and Menjangan. It has a tropical climate, with an average annual temperature and rainfall of 26-27°C and 148.75-188.43 mm, respectively. The wet season extends from October to April, whereas the dry season is from May to September. Bali has a mountainous landscape, especially in the north, where the highest altitude is in Mt. Agung (~3148 m) located in Karangasem district [32].

Bali is divided into 9 districts (administrative level 1, called as "*Kabupaten/Kota*") and 57 sub-districts (administrative level 2, called as "*Kecamatan*") and 176 counties (administrative level 3, called as "*Kelurahan/Desa*"). Bali is inhabited by approximately 4.2 million people living in an area of 5636.7 km$^2$. Bali's capital city Denpasar has the highest population density (~6500 inhabitants per km$^2$), and Buleleng district has the largest area accounting for 24% of the total land (~1365.9 km$^2$). By *kecamatan*, the population was spatially varied ranging from 19,340 (West Selemadeg) to 286,060 people (South Denpasar) and area size ranging from 17.52 (Kuta) to 366.92 km$^2$ (Kintamani). In the present study, we used *kecamatan* as the spatial unit of analysis.

## Data collection

### Dengue notification data

Dengue infection has been a notifiable disease in Indonesia since 1968. All dengue infections (including dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS)) captured by district hospitals must be reported to the District Health Office (DHO) within 24 hours of diagnosis. All cases are then summarized weekly and reported monthly to the Provincial Health Office (PHO) before it is sent to the Indonesian Ministry of Health. Dengue case definitions are applied based on the Indonesian Ministry of Health guidelines [14, 33, 34]. DF is defined as when the patient presents with fever and with two or more of the following symptoms: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, and no evidence of plasma leakage with positive leukopenia [$\leq$ 5000 cells/mm$^3$, thrombocytopenia (platelet count < 150,000 cells/mm$^3$)], an increase in hematocrit (5–10%), and no evidence of plasma loss. DHF is defined as having at least the first two of the following four clinical manifestations: sudden-onset acute fever of 2–7 days duration, spontaneous hemorrhagic manifestations or a positive tourniquet test, hepatomegaly, and circulatory failure, in combination with hematological criteria of thrombocytopenia (<100,000 cells/mm$^3$) and $\geq$20% increased hematocrit. DSS is defined as DHF plus a rapid, weak pulse with narrow pulse pressure ($\leq$20 mmHg), hypotension with cold, clammy skin, and restlessness. Dengue cases are confirmed based on a positive antidengue virus IgM in acute or convalescent serum samples and/or a 4-fold increase in specific IgG antibody titers between the acute and the convalescent samples or virus by isolation or detection of dengue antigen or RNA in serum [34]. In this study, monthly notified dengue cases (DF+DHF+DSS) for each district and *kecamatan* from January 2012 to December 2017 were obtained from the Bali Provincial Health Office (PHO).

## Environmental and population data

The effect of environmental and social factors on the distribution of dengue in Bali was examined. Environmental factors included in this study were rainfall, humidity, temperature, and elevation. Daily meteorological data for the period of January 1, 2012, to December 31, 2017, include total rainfall, annual mean rainfall, humidity, and temperature, which were obtained from three weather stations in Bali. Meteorological data were available online provided by Meteorological, Climatological, and Geophysical Agency (http://dataonline.bmkg.go.id/). The Kriging technique was performed to interpolate meteorological data for the whole Bali island, and the annual mean values for each meteorological data were then sampled for every *kecamatan* by using zonal mean statistics toolbox in GIS software. Data for elevation were extracted from Advanced Spaceborne Thermal Emission and Reflection Radiometer (ASTER) Global Digital Elevation Model (GDEM) Global DEM (30 x 30 m resolution). Additionally, population density for each *kecamatan* obtained from the annual reports provided by the Bureau of Statistics of Bali was also considered in the analysis.

## Descriptive analysis

### Seasonality and trends of dengue notifications

Boxplot of monthly distribution of reported dengue incidence was generated. To assess seasonal patterns and trends in dengue incidence, seasonal trend decomposition with Loess (STL) smoothing [35] was performed using the statistical software R version 3.5.0 package “stlplus” (R Development Core Team, 2017).

## Spatial analysis pipeline

### Visualization of the crude standardized morbidity ratio

Crude standardized morbidity rate (SMR) of dengue infection for each *kecamatan* was calculated by dividing the observed number (*O*) of cases by the expected number (*E*) of cases. The expected cases were estimated by multiplying the total incidence rate for the whole Bali with the population of each corresponding *kecamatan* during the study period. Maps were created to visualize the spatial variation of dengue crude incidence at *kecamatan*-level over the island by using ArcGIS 10.5.1 (ESRI Redlands, CA).

### Exploration of spatial clustering in dengue incidence

Moran’s *I* analysis was carried out to assess the existence of global clustering of the SMR of dengue in Bali during 2012-2017. Before the analysis, a Queen-based spatial contiguity weight matrix (where subdistrict polygon shares a common edge or vertex) was constructed. We did not take into account the five small islands (e.g., Nusa Penida, Nusa Ceningan, Nusa Lembongan, Serangan, and Menjangan) in our analysis, as this could bias spatial weight estimates and thus influence the final results. The values of Moran’s *I* range from -1 to 1; positive value means positive spatial autocorrelation, and negative value means negative spatial autocorrelation, while a value of zero means no spatial autocorrelation, indicating that the disease is randomly distributed [36]. Anselin's LISA analysis was performed to define the type of *kecamatan*, whether it is a high–high (HH) cluster (later stated as high-risk *kecamatan*) or a low–low (LL) cluster (later stated as low-risk *kecamatan*) [37]. The high–high cluster means that *kecamatan* with a high rate nearby another high-rate *kecamatan*, whereas the low–low cluster means that *kecamatan* with a low rate nearby another low-rate *kecamatan*. Both Moran's *I* and LISA analyses were performed using GeoDA v.1.8 software [38].

### Nonspatial modeling

A frequentist nonspatial univariate and multivariable regression model was constructed to identify relationships between dengue incidence and social-environmental factors and select covariates included in the subsequent spatial-temporal modeling. Spearman correlation analysis between covariates was undertaken. To avoid collinearity among environmental predictors, covariates with a correlation coefficient $r \geq |8|$ were not included in the multivariable analysis. Multicollinearity in the final multivariable model was assessed by estimating the variance inflation factor (VIF). Variable with VIF ≥ 4 was dropped from the model. *P*-values of $< 0.05$ were considered to indicate statistical significance. All statistical analyses were carried out by using STATA 15.1 (StataCorp, College Station, TX, USA).

### Spatial and temporal modeling

A Bayesian spatiotemporal model was used to generate a smooth map of dengue relative risk (RR) across the island and examine the relationship between the socio-environmental factors and dengue risk by taking into account spatial autocorrelation. Bayesian statistical software, OpenBUGS version 3.2.3 (Medical Research Council Biostatistics Unit, Cambridge, UK, and Imperial College London, London, UK), was used. This is a Markov chain Monte Carlo

(MCMC) simulation-based software program for performing Bayesian analysis. We built three different models: Model 1 incorporated rainfall, temperature, elevation, and population density as explanatory variables and an unstructured random effect for *kecamatans*; Model II included all explanatory variables in Model I and a spatially structured random effect; and Model III included all of the components of Models I and II.

Observed cases ($O_i$) of dengue for the *i*-th k<u>ecamatan</u> and year *j*¸($i$ = 1,2, …, 57); $j$ = 1, …,6) were assumed to have a Poisson distribution with mean $\mu_i$. The model was formulated as follows:

$$O_{ij} \sim Poisson(\mu_{ij})$$

$$log(\mu_{ij}) = log(E_{ij}) + \theta_{ij}$$

$$\theta_{ij} = \alpha + \beta_1.Temp_{ij} + \beta_2.Rainfall_{ij} + \beta_3.Elev_i + \beta_4.Pop_{ij} + \beta_5.Year\_2013_j + \beta_6.Year\_2014_j + \beta_7.Year\_2015_j + \beta_8.Year\_2016_j + \beta_9.Year\_2017_j + u_i + s_i$$

where $E_{ij}$ is the expected cases in *i*-th *kecamatan* in year *j*; $\theta_{ij}$ is the mean log RR; α is the intercept, $\beta_{1\text{-}5}$ is the coefficients for variable, $\beta_{6\text{-}9}$ is the coefficients for time (years), and $s_i$ is the spatially structured random effect with mean zero and variance $\sigma_s^2$; $u_i$ represents the unstructured random effect (assumed to have a mean zero and variance $\sigma_s^2$). The spatially structured random effect was modeled using conditional autoregressive (CAR) prior structure. An adjacency weight matrix was constructed to determine spatial relationships between *kecamatan*. If two *kecamatan*s share a border, it was assumed that weight = 1 and, if they do not, then weight = 0. The adjacency matrix was constructed using the “Adjacency for WinBUGS Tool” (<u>https://www.umesc.usgs.gov/management/dss/adjacency_tool.html</u>), which runs in ArcGIS software. A flat prior distribution was specified for the intercept, whereas a normal prior distribution was used for the coefficients (with a mean = 0 and a precision = 0.0001). The priors for the precision ($1/\sigma_t^2$) of spatially structured random effects were specified using noninformative gamma distributions (0.1, 0.1).

Environmental, social, and time covariates were included in the model as fixed effects and a CAR random effect. Standardization of all environmental variables was performed to allow comparability of the effects (providing a more meaningful interpretation of the results) and to improve model fit. Standardization involved subtracting the mean from each environmental variable, and the difference was divided by the standard deviation, which resulted in a standard deviation of one.

An initial burn-in of 5,000 iterations was used, followed by 20,000 iterations, where values for the intercept, coefficients, and predicted probability of infection at the prediction locations were stored. We assessed the convergence of each variable by visually observing the history and density plots; convergence was successfully achieved after approximately 120,000 iterations for each model. The outputs of Bayesian models, including parameter estimates and spatial prediction at unsampled locations, are distributions termed as posterior distributions. These posterior distributions represent fully the uncertainties associated with the parameter estimates. The deviance information criterion (DIC) was used to compare the goodness-of-fit between models, where a lower DIC indicates a better model fit. We summarized the posterior distributions in terms of the posterior mean and 95% Bayesian credible interval (CrI). The posterior distributions of RR of the best-fitted model were mapped by using GIS software ArcGIS 10.5 (ESRI, Redlands, CA).

## 3. Results

### Descriptive analysis

We analyzed a total of 55,963 dengue infection cases reported during 2012-2017 in Bali. In general, there was a substantial increase in the number of notified dengue cases since 2012, with the highest cases was reported in 2016 (21,668 cases) (Table 1). A high incidence was reported during the first semester of the year, and the highest incidence was identified during April/May, whereas the lowest incidence was recorded in October (Fig. 1). The STL plot revealed strong seasonality in dengue incidence and showed an upward trend in incidence during 2012-2017 (Fig. 2).

**Table 1.** Summary statistics of the number of notified dengue cases and incidence (per 100,000 people) in Bali during 2012-2017

| Year | Number of cases | Monthly statistics | | | | Incidence (per 100,000 people) |
|---|---|---|---|---|---|---|
| | | Mean | Minimum | Maximum | S.D. | |
| 2012 | 2650 | 220.83 | 83 | 389 | 122.75 | 65.90 |
| 2013 | 6813 | 567.75 | 261 | 960 | 261.43 | 168.48 |
| 2014 | 8629 | 719.08 | 318 | 1087 | 310.08 | 204.23 |
| 2015 | 10704 | 892 | 212 | 1685 | 581.85 | 257.75 |
| 2016 | 21668 | 1805.67 | 919 | 3414 | 876.05 | 515.90 |
| 2017 | 4499 | 374.91 | 100 | 809 | 261.74 | 105.95 |

At *kecamatan* level, the crude SMRs of dengue was spatially heterogeneous across the island (Fig. 3). The highest crude standardized morbidity rates (SMR) of dengue was observed in Mengwi (*Kecamatan* Badung) and Ubud (*Kecamatan* Gianyar). *Kecamatan* Buleleng, Karangasem, Bebandem, Banjarakan, and Bangli were also found to have high crude SMRs during the period studied.

### Spatial autocorrelation

We identified significant positive spatial autocorrelation for dengue incidence at the *kecamatan* level during 2012-2017. Moran's *I* values ranged from 0.148 to 0.743 (Table 2), indicating that dengue incidence was geographically clustered. However, the spatial autocorrelation index showed a declining trend, with the lowest value observed in 2017 (Moran's $I = 0.148$; $P < 0.05$).

Based on LISA analysis, high–high (HH) *kecamatans* were observed in the south during 2012, covering all *kecamatans* of Denpasar, 5 *kecamatans* in south Badung, and *kecamatan* Kediri in Tabanan district (Fig. 4). Changes in the distribution of high-risk *kecamatans* were observed since 2014 when the high-risk cluster moved toward 5 *kecamatans* in south Gianyar, 3 *kecamatans* in Karangasem and 1 *kecamatan* in Klungkung. Most low–low (LL) *kecamatans* were found in the west and central part of the island.

**Table 2.** Spatial autocorrelation analysis for annual dengue incidence in Bali, 2012-2017

| Year | Moran's *I* | *P*-value |
|---|---|---|
| 2012 | 0.743 | 0.001 |
| 2013 | 0.414 | 0.001 |
| 2014 | 0.219 | 0.004 |
| 2015 | 0.271 | 0.002 |
| 2016 | 0.231 | 0.005 |
| 2017 | 0.148 | 0.041 |

## Spatial modeling and risk prediction

Pairwise Pearson correlation analysis indicated that humidity was strongly associated with temperature ($r=-0.89$, $P < 0.05$) (Supplementary Table S1). Thus, we did not included humidity in the model to avoid collinearity. Both univariate and multivariate regression analyses demonstrated that year, rainfall, temperature, elevation, and population density were significantly associated with dengue incidence (Supplementary Table S2).

Based on DIC estimates, Model III (which contained the Bayesian model with both the unstructured and spatially structured random effect) had the lowest DIC value (DIC=222.9), indicating the best-fitted model for dengue compared to the other models (Table 3). In this Model III, the dengue risk was positively significantly associated with rainfall and population density. The best-fitted CAR model showed increased log RR of dengue in *kecamatans* with high total annual rainfall (log RR: 0.18 for each 1-mm increase in rainfall; 95% CrI: 0.05-0.32) and high population density (log RR: 2.13 per 1000 people/sq.km increase; 95% CrI: 1.27-2.99). The association between temperature and dengue risk was found to be insignificant. The log RR of dengue was decreased in *kecamatans* with higher elevation (log RR: 0.28 for each 1-m increase in elevation; 95% CrI: 0.02-0.54). In addition, no significant association was observed between dengue RR and year except in 2014. The log RR in 2014 was significantly lower (log RR: 0.63; 95% CrI: 0.04-1.23) than the reference (2012).

The RRs of dengue ranged from 1.05 to 10.54 across Bali (Fig. 5), with the highest RR identified in *kecamatans* in southeast Karangasem district, Bangli and Buleleng. The map of the posterior means of the spatially structured random effects showed evidence of spatial clustering after accounting for covariates covering *kecamatans* in Karangasem, Klungkung and Bangli, whereas the unstructured random effects showed a spatially random pattern (Supplementary Fig. S1). High standard deviation was observed in *kecamatans* in the east and northwest parts of the island (Supplementary Fig. S2), which also correlated with the *kecamatans* that exhibited a high RR.

**Table 3.** Regression coefficients and 95% credible interval (CrI) from Bayesian nonspatial and spatial models for dengue in Bali

| **Variable** | **Coefficient posterior mean (95% CrI)** | | |
|---|---|---|---|
| | **Model I[a]** | **Model II[b]** | **Model III[c]*** |
| α (Intercept) | -0.26 (-0.81 to 0.28) | -0.18 (-0.65 to 0.28) | -0.19 (-0.72 to 0.31) |
| Total annual rainfall (mm) | 0.21 (0.08 to 0.35) | 0.14 (0.03 to 0.27) | 0.18 (0.05 to 0.32) |
| Annual maximum temperature (°C) | 1.5 x $10^{-2}$ (-0.19 to 0.19) | -0.03 (-0.20 to 0.12) | -0.03 (-0.21 to 0.14) |
| Mean elevation (m) | -0.40 (-0.62 to -0.17) | -0.30 (-0.58 to -0.02) | -0.28 (-0.54 to -0.02) |
| Population density (1000 persons/sq.km) | 2.06 (1.26 to 2.91) | 2.07 (1.10 to 3.01) | 2.13 (1.27 to 2.99) |
| Time (year) | | | |
| 2012 | Ref | Ref | Ref |
| 2013 | 0.43 (-0.16 to 1.03) | 0.31 (-0.15 to 0.79) | 0.35 (-0.19 to 0.91) |
| 2014 | -0.59 (-1.24 to 0.06) | -0.63 (-1.17 to -0.08) | -0.63 (-1.23 to -0.04) |
| 2015 | -0.02 (-0.65 to 0.63) | -0.08 (-0.64 to 0.45) | -0.02 (-0.63 to 0.60) |
| 2016 | -0.51 (-1.18 to 0.15) | -0.07 (-1.22 to -0.08) | -0.53 (-1.14 to 0.10) |
| 2017 | -0.09 (-0.75 to 0.56) | -0.08 (-0.62 to 0.47) | -0.09 (-0.69 to 0.50) |
| Heterogeneity unstructured | 2.63 (1.48 to 4.23) | - | 5.71 (2.07 to 16.09) |
| Heterogeneity structured | - | 0.86 (0.47 to 1.41) | 4.02 (0.79 to 14.78) |
| DIC | 418.2 | 316.4 | 222.9 |

[a] unstructured; [b] structured; [c] unstructured and structured; * best-fit model; DIC, deviance information criteria

## 4. Discussion

Using recent dengue notification data, to the best of our knowledge, this was the first ecological study on assessing the spatial and temporal pattern of dengue as well as quantifying factors associated with the incidence of dengue in the world-renowned tropical island of Bali. Our findings demonstrated that, in general, the dengue incidence was spatially clustered and the most high-risk *kecamatans* were identified along the lowlands areas in the south and east coast covering all *kecamatans* in the Denpasar metropolitan area, Badung, Tabanan, Gianyar, Klungkung, and Karangasem district. Indeed, the results from this study showed that socio-ecological factors including climate, elevation, and population density played an important role in the spatial and temporal pattern of dengue risk in the island.

Our study demonstrated a strong seasonality trend in dengue incidence, with most dengue cases reporting during December to April, which coincided with the rainy season [39]. During the rainy season, a large amount of water bodies exist, and thus, they provide tremendous opportunity for *Aedes* mosquitoes to complete their aquatic stage and maintain their population in the environment. In addition, lowland areas in south Bali were often affected by flooding following heavy rainfall due to insufficient drainage system [40] and poor waste management [41]. Rainwater accumulated in any container including both natural and manmade containers (including bottles, cans, open sewage, and tires) is known to be a potential larval habitat for the mosquitoes *A. aegypti* and *A. albopictus* [42]. Studies on the association of vector abundance and season in an island setting have also been described elsewhere [43, 44]. Our findings highlight the need for timely integrated vector-control strategies during both wet and dry seasons by controlling immature *Aedes* mosquitoes through routine inspection on potential breeding sites and improving sanitation and waste management. From a travel medicine perspective, travel to

Bali during this period may increase the likelihood of dengue infection. Therefore, travelers should consider taking necessary health preventive measures (e.g., repellents or bed nets) and future reliable vaccination to minimize risk.

Our analysis identified clustering in the incidence of dengue spatially and temporally during the period studied. However, the propensity for dengue clustering in the island of Bali appears to reduce during the 5-year period, which means that the distribution of high-risk areas becomes randomly spread over the island. This finding could be due to dynamic changes in local socio-ecological factors and the effect of ongoing control measures that have been undertaken at the local level. The spread of the high-risk cluster was initially identified in the southern *kecamatans* including all *kecamatans* in Denpasar city, Badung district, and *kecamatan* Tabanan, before it expanded to *kecamatans* in the east coast of the island (e.g., *kecamatan* Karangasem, Abang, Babandem, and Gianyar) in 2016. Such changes appear to be driven by human migration and local environment and socioeconomic conditions. Bali is relatively a small island in which the distance between districts or *kecamatans* is relatively close and thus allow people to commute easily. This frequent mobilization may facilitate the spread of the infection easily from one community to another. Further studies, however, are needed to investigate the effect of migration (inland travel) on the control of dengue transmission within the island.

Additionally, these lowland areas also known to be a favorite destination that provides attractive landscapes for international tourists, such as beaches, irrigated rice fields, rainforest, cultural heritage sites, and temples. Moreover, approximately 2 million people residing in this southern area account for 50% of Bali’s total population [32], and 4 million tourists visit this place annually. Tourism might have partly driven dengue transmission in the island [45]. The increased flow of incoming travelers originating from various levels of dengue endemicity toward Bali is likely to have increase dengue transmission in recent years, as it might have facilitated the spillover of DENV strains between travelers and local Balinese [15], which was evidenced by a dramatic shift in the diversity of DENV serotypes in Bali since 2011 [17, 18]. A vast number of studies have documented the dengue infection acquired by travelers who returned from this island [17, 19, 46], highlighting the Bali as a source of dengue transmission in the region. Our findings suggest the need for strengthening disease control in touristic areas in Bali, travel medicine recommendations, and surveillance targeting tourists visiting Bali island.

Our results indicate that the geographical distribution of DENV infection in Bali is influenced by the complex interaction between climatic, environmental, and population factors. In our analysis, we found that rainfall was positively associated with spatial variation in risk for dengue in Bali. This finding was consistent with those of other studies conducted in Yogyakarta [29], Timor Leste [47], and Colombia [48]. Our results indicate an increase in the RR of dengue by every unit increase in the annual precipitation. In contrast, the effect of temperature on the heterogeneity of risk of dengue over Bali was not evident compared to the effect of rainfall. This could be due to the small variation in temperature across kecamatans in Bali. Our study also supports other findings in Yogyakarta [29], which found no significant effect of temperature variability on the dengue incidence. Studies show that mosquitoes required a temperature of 25-30°C for their optimal development [49]. Bali has a mean annual temperature ranging from 26 to 27°C and average humidity ranging from 79% to 85% [32], which is favorable for mosquito survival. Our study also identified the negative relationship between elevation and dengue incidence, which confirmed that the risk of dengue is relatively high in *kecamatans* located at the lowland area. This relationship is also observed in other parts of Indonesia [29]. It has been known that elevation is closely related to climate, which is the fundamental variable for mosquito propagation. Furthermore, our findings showed that population density was significant factor associated with variation in dengue risk in the island. The RR was higher in the much dense *kecamatans*; this could be explained by the availability of a more favorable habitat (e.g., water containers) nearby human settlements, and this led to higher mosquito density and longer survival rate [50]. These results support the presumption that increasing urbanization would increase the risk of dengue transmission. Increased dengue transmission has also been reported to be associated with high population density elsewhere [51].

Our predictive map showed that after controlling for environmental factors, the highest RR of dengue was found in Karangasem, Bangli, and Buleleng. Although inconsistent with our crude incidence map, these findings have important operational implications in the way that dengue control can be deployed locally. Local health authorities should be aware of the potential risk factors that may directly or indirectly facilitate dengue transmission in these high-risk *kecamatans*. Water scarcity has become an issue in Bali during the last few years due to increased water demand, as Bali’s tourism industry is rocketing [52, 53]; this has largely affected the local Balinese, especially in suburban areas. During the dry season, households that have limited access to pipe water, especially in urban and peri-urban such as in Buleleng, may greatly rely on other sources (e.g., rainwater, boreholes) and tend to use containers to store water for their daily needs, which more likely increases infestation of *A. aegypti* and *A. albopictus* [54, 55]. In addition, the Balinese community has strong sociocultural practices related to water; for instance, households often have a water container for their “holy water” (known as *Air Tirta*) in their home, and most temples in Bali had pools for their religious practices. Such behaviors may have played an important role in maintaining vector abundance in the environment. Economic and tourism growth have generated rapid land use conversion from paddy fields into built-up areas and human settlements [52], which could provide more mosquito habitats and increase human-vector contact rates. Climate and land cover could also partly explain the high predicted dengue RR in these areas. Both areas, Bangli and Karangasem, have similarity in climate and land cover. The annual precipitation rate in Bangli tends to be higher relative to that in other areas in Bali [32], as it is located in the mountainous zone. In the lowland areas in Bangli, Buleleng, and Karangasem, forested land, plantations, and rainfed paddy fields are common and very close to the human settlements. This condition provides a favorable habitat for the secondary vector of the dengue fever *A. albopictus* mosquito [56]. Furthermore, a nationwide basic health survey in 2013 indicated that 41% of Balinese households used coil to prevent mosquito bite, with a high proportion found in Gianyar, Buleleng, and Klungkung [40], which may likely increase mosquito resistance against common insecticides [57] and thus hinder the effectiveness of vector control programs in these areas. Indeed, our predictive map also shows that high-risk areas were on the outside of Denpasar metropolitan city, which means that a relatively high incidence in Denpasar might partly be due to people migrating from those high-risk areas who seek for better economy. Intervention strategies including promoting community-based vector control and health education as well as improving access to health services, sanitation, and waste management should be more directed in these predicted high-risk areas.

Some climatic and environmental factors assessed in this study influenced the spatial variability of dengue in Bali; however, we also noticed significant residual spatial variation indicating some unmeasured factors, which could partially influence geographical patterns of dengue incidence in Bali, such as water storage behavior, sanitation, vector control measures, and traveling pattern. In addition, our findings also showed a high standard deviation in high RR areas, which indicates high uncertainty in the model. Therefore, further local epidemiological surveys, especially in

Karangasem, southern Bangli, and Buleleng, should be conducted to reveal the local socio-ecological factors that are associated with dengue transmission to better inform local health authorities on planning and implementing effective control strategies.

The results of the study should be interpreted in light of some study limitations. First, this study used reported dengue cases captured through passive surveillance (hospitals), which may not represent the actual dengue infection in the population, and hence, the results may be underestimated. Second, variation in the quality and completeness of the reported dengue data from each *kecamatan* may also likely impact the geographical variation of the disease incidence of dengue in Bali. It is important to note that incompleteness and variation in reporting procedures remain an important issue in the dengue surveillance system in Indonesia [58]. In addition, the accuracy and variation of the data could also be influenced by a varied level of awareness on dengue fever among local physicians to diagnose dengue, Balinese health-seeking behavior, and dengue confirmation approaches. These factors, in turn, could potentially lead to under/over-reported dengue cases and thus may lead to bias in our analysis. However, as this study used time-series data and was primarily focused on the seasonality and the spatial distributions of disease, these potential imperfections in the data should not significantly influence the findings. Third, this study was an ecological study and solely focused on the effects of climate and environment. There might be potential confounding factors at the *kecamatan* level that were not included in this study, which may have affected our findings. Data for urbanization rate, human migration, vector density, drinking water infrastructure, and control measures that undergone at the *kecamatan* level were not available; therefore, we were not able to take these variables into consideration into the model. Fifth, during the epidemic, dengue cases were commonly classified by clinical and epidemiological criteria particularly in resource-limited settings. Although local physicians were very familiar with dengue fever clinical diagnosis, laboratory diagnosis is not generally and routinely performed in every health provider across Bali due to its cost. Given that inadequacy and variation in diagnostic capacity and the nature of dengue infection (i.e., broad clinical manifestations, which exhibit similar symptoms as those of other arboviral diseases), other emerging/re-emerging vector-borne diseases that also exist in Bali include Chikungunya [21, 59] and Zika virus disease [60, 61], which may likely be misdiagnosed and reported as dengue and that might influence the findings of this study. Therefore, further local epidemiological surveys are highly needed especially focusing on dengue high-risk *kecamatans* identified in this study to provide more robust predictive maps as well as to help ascertain dengue and other arboviruses in Bali.

## Conclusion

In general, geographical distribution of dengue incidence in Bali was spatially clustered along the south toward the eastern part of the island, and the incidence of dengue in Bali was strongly seasonal, with most incidence reported during January to May. Local weather and socioecological condition including rainfall, elevation, and population density were associated with spatial and temporal dynamics of dengue across the island. Locally enhanced disease surveillance and targeted intervention strategies should be prioritized in the high-risk *kecamatans* identified in this study to control dengue transmission as well as other arboviruses in the island of Bali. From a travel medicine standpoint, this study provides useful information for travelers as well as health authorities in the region. Travelers may consider taking immunization before travelling to Bali, especially during the high dengue endemic season. In addition, it is highly recommended that they use protection such as insect repellent during their visit. Travel advice should be delivered by the local health authorities to prepare travelers before visiting Bali. Moreover, this finding may also be beneficial as foundation for strengthening regional dengue early-warning systems and surveillance.

## Ethical approval and consent to participate

The research protocol of this study was reviewed and approved by the Health Research Ethics Committee of National Institute for Health Research and Development (LB.02.01/2/KE.232/2018). All dengue cases were anonymized and aggregated to *kecamatan*-level before the commencement of analysis. No personal identifiers were presented, and maps presented in this paper do not show patients' addresses. Signing of a consent form was not necessary, as secondary data were used.

## Data availability

Data are available at the Provincial Health Agency (PHA) and Directorate General for Disease Prevention and Control, Indonesian Ministry of Health, for researchers who meet the criteria for access to the data.

## Funding

None.

## Competing interests

The authors declare that they have no competing interests.

## Acknowledgments

The authors are grateful to the Bali Provincial Health Agency (PHA) and Directorate General for Disease Prevention and Control, Indonesian Ministry of Health, for providing us with the data on reported dengue cases in Bali from 2012 to 2017.

## Author Contributions

Conceptualization: P.W.D, W.H., R.J.S.M
Data curation: P.W.D, R.M, E.P
Formal analysis: P.W.D, R.J.S.M, W.B
Investigation: P.W.D, R.M, T.P
Methodology: P.W.D, R.J.S.M, W.H
Project administration: P.W.D, R.M, M.H., J.A
Resources: P.W.D, R.M
Software: P.W.D
Supervision: R.J.S.M, W.H
Validation: P.W.D, R.M, R.J.S.M
Visualization: P.W.D
Writing original draft and final manuscript: P.W.D
Writing – review and editing: R.M, T.P, J.A, E.P, M.H, W.H, R.J.S.M

## References

1. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature 2013;496(7446):504-7. https://doi.org/10.1038/nature12060.
2. Simmons CP, Farrar JJ, Nguyen v V, Wills B. Dengue. N Engl J Med 2012;366(15):1423-32. https://doi.org/10.1056/NEJMra1110265.

3. Kraemer MU, Sinka ME, Duda KA, Mylne AQ, Shearer FM, Barker CM, et al. The global distribution of the arbovirus vectors *Aedes aegypti* and *Ae. albopictus*. eLife 2015;4:e08347. https://doi.org/10.7554/eLife.08347.
4. Tian H, Sun Z, Faria NR, Yang J, Cazelles B, Huang S, et al. Increasing airline travel may facilitate co-circulation of multiple dengue virus serotypes in Asia. PLoS Neglected Trop Dis 2017;11(8):e0005694. https://doi.org/10.1371/journal.pntd.0005694.
5. Guzman A, Isturiz RE. Update on the global spread of dengue. Int J Antimicrob Agents 2010;36 Suppl 1:S40-2. https://doi.org/10.1016/j.ijantimicag.2010.06.018.
6. Choe YJ, Choe SA, Cho SI. Importation of travel-related infectious diseases is increasing in South Korea: An analysis of salmonellosis, shigellosis, malaria, and dengue surveillance data. Trav Med Infect Dis 2017;19:22-7. doi: https://doi.org/10.1016/j.tmaid.2017.09.003.
7. Liu Y, Liu J, Cheng G. Vaccines and immunization strategies for dengue prevention. Emerging Microbes Infect 2016;5(7):e77. https://doi.org/10.1038/emi.2016.74.
8. Halstead SB. Dengue vaccine development: a 75% solution? Lancet 2012;380(9853):1535-6. https://doi.org/10.1016/s0140-6736(12)61510-4.
9. Arredondo-García JL, Hadinegoro SR, Reynales H, Chua MN, Rivera Medina DM, Chotpitayasunondh T, et al. Four-year safety follow-up of the tetravalent dengue vaccine efficacy randomized controlled trials in Asia and Latin America. Clin Microbiol Infect 2018;24(7):755-63. https://doi.org/10.1016/j.cmi.2018.01.018.
10. L'Azou M, Moureau A, Sarti E, Nealon J, Zambrano B, Wartel TA, et al. Symptomatic Dengue in Children in 10 Asian and Latin American Countries. N Engl J Med 2016;374(12):1155-66. https://doi.org/10.1056/NEJMoa1503877.
11. Flasche S, Jit M, Rodríguez-Barraquer I, Coudeville L, Recker M, Koelle K, et al. The Long-Term Safety, Public Health Impact, and Cost-Effectiveness of Routine Vaccination with a Recombinant, Live-Attenuated Dengue Vaccine (Dengvaxia): A Model Comparison Study. PLoS Medicine. 2016;13(11):e1002181. https://doi.org/10.1371/journal.pmed.1002181.
12. Wichmann O, Vannice K, Asturias EJ, de Albuquerque Luna EJ, Longini I, Lopez AL, et al. Live-attenuated tetravalent dengue vaccines: The needs and challenges of post-licensure evaluation of vaccine safety and effectiveness. Vaccine. 2017;35(42):5535-42. https://doi.org/10.1016/j.vaccine.2017.08.066.

13. World Health Organization. Global Strategy For Dengue Prevention And Control, 2012–2020. Geneva: WHO Press.
14. Sumarmo. Dengue haemorrhagic fever in Indonesia. Southeast Asian J Trop Med Public Health 1987;18(3):269-74.
15. Karyanti MR, Uiterwaal CS, Kusriastuti R, Hadinegoro SR, Rovers MM, Heesterbeek H, et al. The changing incidence of dengue haemorrhagic fever in Indonesia: a 45-year registry-based analysis. BMC Infect Dis 2014;14:412. https://doi.org/10.1186/1471-2334-14-412.
16. Ministry of Health Republic of Indonesia. Indonesia Health Profile 2017. Jakarta: Ministry of Health Republic of Indonesia; 2018.
17. Ernst T, McCarthy S, Chidlow G, Luang-Suarkia D, Holmes EC, Smith DW, et al. Emergence of a New Lineage of Dengue Virus Type 2 Identified in Travelers Entering Western Australia from Indonesia, 2010-2012. PLoS Neglected Trop Dis 2015;9(1). https://doi.org/10.1371/journal.pntd.0003442.
18. Megawati D, Masyeni S, Yohan B, Lestarini A, Hayati RF, Meutiawati F, et al. Dengue in Bali: Clinical characteristics and genetic diversity of circulating dengue viruses. PLoS Neglected Trop Dis 2017;11(5). https://doi.org/10.1371/journal.pntd.0005483.
19. Sohail A, McGuinness SL, Lightowler R, Leder K, Jomon B, Bain CA, et al. Spectrum of illness among returned Australian travellers from Bali, Indonesia: a 5□year retrospective observational study. Intern Med J 2018. https://doi.org/10.1111/imj.13993.
20. Zavattoni M, Rovida F, Campanini G, Percivalle E, Sarasini A, Cristini G, et al. Miscarriage following dengue virus 3 infection in the first six weeks of pregnancy of a dengue virus-naive traveller returning from Bali to Italy, April 2016. Eurosurveillance 2016;21(31):30308. https://doi.org/10.2807/1560-7917.ES.2016.21.31.30308.
21. Yoshikawa MJ, Kusriastuti R. Surge of dengue virus infection and chikungunya fever in Bali in 2010: The burden of mosquito-borne infectious diseases in a tourist destination. Trop Med Health 2013;41(2):67-78. https://doi.org/10.2149/tmh.2011-05.
22. Provincial Bureau of Statistics of Bali. Statistics of International Tourists arrived in Bali 2016. Denpasar: Provincial Bureau of Statistics of Bali; 2016.
23. Masyeni S, Yohan B, Somia IKA, Myint KSA, Sasmono RT. Dengue infection in international travellers visiting Bali, Indonesia. J Travel Med 2018;25(1):tay061-tay. https://doi.org/10.1093/jtm/tay061.

24. Ernst T, McCarthy S, Chidlow G, Luang-Suarkia D, Holmes EC, Smith DW, et al. Emergence of a new lineage of dengue virus type 2 identified in travelers entering Western Australia from Indonesia, 2010-2012. PLoS Neglected Trop Dis 2015;9(1):e0003442. https://doi.org/10.1371/journal.pntd.0003442.
25. Palaniyandi M. The role of remote sensing and GIS for spatial prediction of vector-borne diseases transmission: a systematic review. J Vector Borne Dis 2012;49(4):197-204.
26. Kalluri S, Gilruth P, Rogers D, Szczur M. Surveillance of arthropod vector-borne infectious diseases using remote sensing techniques: a review. PLoS Pathogens 2007;3(10):1361-71. https://doi.org/10.1371/journal.ppat.0030116.
27. Dhewantara PW, Ruliansyah A, Fuadiyah ME, Astuti EP, Widawati M. Space-time scan statistics of 2007-2013 dengue incidence in Cimahi City, Indonesia. Geospat Health 2015;10(2):373. https://doi.org/10.4081/gh.2015.373.
28. Wijayanti SPM, Porphyre T, Chase-Topping M, Rainey SM, McFarlane M, Schnettler E, et al. The Importance of Socio-Economic Versus Environmental Risk Factors for Reported Dengue Cases in Java, Indonesia. PLoS Neglected Trop Dis 2016;10(9):e0004964. https://doi.org/10.1371/journal.pntd.0004964.
29. Kesetyaningsih TW, Andarini S, Sudarto, Pramoedyo H. Determination of environmental factors affecting dengue incidence in Sleman districti Yogyakarta Indonesia. African J Infect Dis 2018;12(1 Suppl):13-25. https://doi.org/10.2101/Ajid.12v1S.3.
30. Astuti EP, Dhewantara PW, Prasetyowati H, Ipa M, Herawati C, Hendrayana K. Paediatric dengue infection in Cirebon, Indonesia: a temporal and spatial analysis of notified dengue incidence to inform surveillance. Parasites Vectors 2019;12(1):186. https://doi.org/10.1186/s13071-019-3446-3.
31. Husnina Z, Clements ACA, Wangdi K. Forest cover and climate as potential drivers for dengue fever in Sumatra and Kalimantan 2006-2016: A spatiotemporal analysis. Trop Med Int Health 2019. https://doi.org/10.1111/tmi.13248.
32. Bali in Figures 2017 [Internet]. Provincial Bureau of Statistics of Bali. 2017. Available from: https://bali.bps.go.id/publication.
33. World Health Organization. Dengue Haemorrhagic Fever: Diagnosis, treatment, prevention and control: World Health Organization. Geneva: World Health Organization; 1997.

34. Ministry of Health Republic of Indonesia. Guidelines on dengue prevention and control in healthcare facilities in Indonesia. Jakarta: Ministry of Health Republic of Indonesia; 2005.
35. Cleveland RB, Cleveland WS, McRae JE, Terpenning I. STL: A Seasonal-Trend Decomposition. Journal of Official Statistics 1990;6(1):3-73.
36. Moran PAP. Notes on Continuous Stochastic Phenomena. Biometrika 1950;37(1/2):17-23. https://doi.org/10.2307/2332142.
37. Anselin L. Local Indicators of Spatial Association—LISA. Geogr Anal. 1995;27(2):93-115. https://doi.org/10.1111/j.1538-4632.1995.tb00338.x.
38. Anselin L, Syabri, I., Kho, Y. GeoDa, an introduction to spatial data analysis. Geogr Anal 2006;38:5-22.
39. Azhar K, Marina R, Anwar A. A prediction model of dengue incidence using climate variability in Denpasar city. Health Science J Indonesia 2017;8(2):68-73.
40. Pranata S, Fauziah Y, Budisuari MA, Kusrini I. Riskesdas dalam angka Provinsi Bali 2013. Jakarta: Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan RI; 2013.
41. MacRae G. Solid waste management in tropical Asia: what can we learn from Bali? Waste Manage Res 2012;30(1):72-9. https://doi.org/10.1177/0734242x10386138.
42. Urdaneta-Marquez L, Failloux A-B. Population genetic structure of *Aedes aegypti*, the principal vector of dengue viruses. Infect Genet Evol 2011;11(2):253-61. https://doi.org/10.1016/j.meegid.2010.11.020.
43. Regis LN, Acioli RV, Silveira JC, de Melo-Santos MAV, da Cunha MCS, Souza F, et al. Characterization of the spatial and temporal dynamics of the dengue vector population established in urban areas of Fernando de Noronha, a Brazilian oceanic island. Acta Trop 2014;137:80-7. https://doi.org/10.1016/j.actatropica.2014.04.010.
44. Sirisena P, Noordeen F, Kurukulasuriya H, Romesh TA, Fernando L. Effect of Climatic Factors and Population Density on the Distribution of Dengue in Sri Lanka: A GIS Based Evaluation for Prediction of Outbreaks. PloS One 2017;12(1):e0166806. https://doi.org/10.1371/journal.pone.0166806.
45. de Jong W, Rusli M, Bhoelan S, Rohde S, Rantam FA, Noeryoto PA, et al. Endemic and emerging acute virus infections in Indonesia: an overview of the past decade and implications for the future. Crit Rev Microbiol 2018:1-17. https://doi.org/10.1080/1040841x.2018.1438986.

46. Saito M, Tamayose M, Miyagi K, Takaragawa H, Tateyama M, Tadano M, et al. Serologic and virologic studies of an imported dengue case occurring in 2014 in Okinawa, Japan. Jpn J Infect Dis 2016;69(1):60-5. https://doi.org/10.7883/yoken.JJID.2015.061.
47. Wangdi K, Clements ACA, Du T, Nery SV. Spatial and temporal patterns of dengue infections in Timor-Leste, 2005–2013. Parasites Vectors 2018;11(1):9. https://doi.org/10.1186/s13071-017-2588-4.
48. Restrepo AC, Baker P, Clements ACA. National spatial and temporal patterns of notified dengue cases, Colombia 2007–2010. Trop Med Int Health 2014;19(7):863-71. https://doi.org/10.1111/tmi.12325.
49. Koch LK, Cunze S, Werblow A, Kochmann J, Dorge DD, Mehlhorn H, et al. Modeling the habitat suitability for the arbovirus vector *Aedes albopictus* (Diptera: Culicidae) in Germany. Parasitol Res 2016;115(3):957-64. https://doi.org/10.1007/s00436-015-4822-3.
50. Li Y, Kamara F, Zhou G, Puthiyakunnon S, Li C, Liu Y, et al. Urbanization increases Aedes albopictus larval habitats and accelerates mosquito development and survivorship. PLoS Neglected Trop Dis 2014;8(11):e3301. https://doi.org/10.1371/journal.pntd.0003301.
51. Qi X, Wang Y, Li Y, Meng Y, Chen Q, Ma J, et al. The Effects of Socioeconomic and Environmental Factors on the Incidence of Dengue Fever in the Pearl River Delta, China, 2013. PLoS Neglected Trop Dis 2015;9(10):e0004159. https://doi.org/10.1371/journal.pntd.0004159.
52. Cole S. Tourism and water: from stakeholders to rights holders, and what tourism businesses need to do. J Sustainable Tourism 2014;22(1):89-106. https://doi.org/10.1080/09669582.2013.776062.
53. Strauß S. Water Conflicts among Different User Groups in South Bali, Indonesia. Human Ecology 2011;39(1):69-79. https://doi.org/10.1007/s10745-011-9381-3.
54. Vannavong N, Seidu R, Stenstrom TA, Dada N, Overgaard HJ. Effects of socio-demographic characteristics and household water management on Aedes aegypti production in suburban and rural villages in Laos and Thailand. Parasites Vectors 2017;10(1):170. https://doi.org/10.1186/s13071-017-2107-7.

55. Wijayanti SP, Sunaryo S, Suprihatin S, McFarlane M, Rainey SM, Dietrich I, et al. Dengue in Java, Indonesia: Relevance of Mosquito Indices as Risk Predictors. PLoS Neglected Trop Dis 2016;10(3):e0004500. https://doi.org/10.1371/journal.pntd.0004500.
56. Higa Y. Dengue Vectors and their Spatial Distribution. Trop Med Health 2011;39(4 Suppl):17-27. https://doi.org/10.2149/tmh.2011-S04.
57. Hamid PH, Prastowo J, Widyasari A, Taubert A, Hermosilla C. Knockdown resistance (kdr) of the voltage-gated sodium channel gene of Aedes aegypti population in Denpasar, Bali, Indonesia. Parasites Vectors 2017;10(1):283. https://doi.org/10.1186/s13071-017-2215-4.
58. Wahyono TYM, Nealon J, Beucher S, Prayitno A, Moureau A, Nawawi S, et al. Indonesian dengue burden estimates: review of evidence by an expert panel. Epidemiol Infection 2017;145(11):2324-9. https://doi.org/10.1017/s0950268817001030.
59. Sari K, Myint KSA, Andayani AR, Adi PD, Dhenni R, Perkasa A, et al. Chikungunya fever outbreak identified in North Bali, Indonesia. Trans R Soc Trop Med Hyg 2017;111(7):325-7. https://doi.org/10.1093/trstmh/trx054.
60. Aditya P, Frilasita Y, Sotianingsih H, Rahma FH, Chairin Nisa Mr, Ungke A, et al. Isolation of Zika Virus from Febrile Patient, Indonesia. Emerg Infect Dis 2016;22(5):924. https://doi.org//10.3201/eid2205.151915.
61. Leung GH, Baird RW, Druce J, Anstey NM. Zika virus infection in Australia following a monkey bite in Indonesia. Southeast Asian J Trop Med Public Health 2015;46(3):460-4.

## List of figures

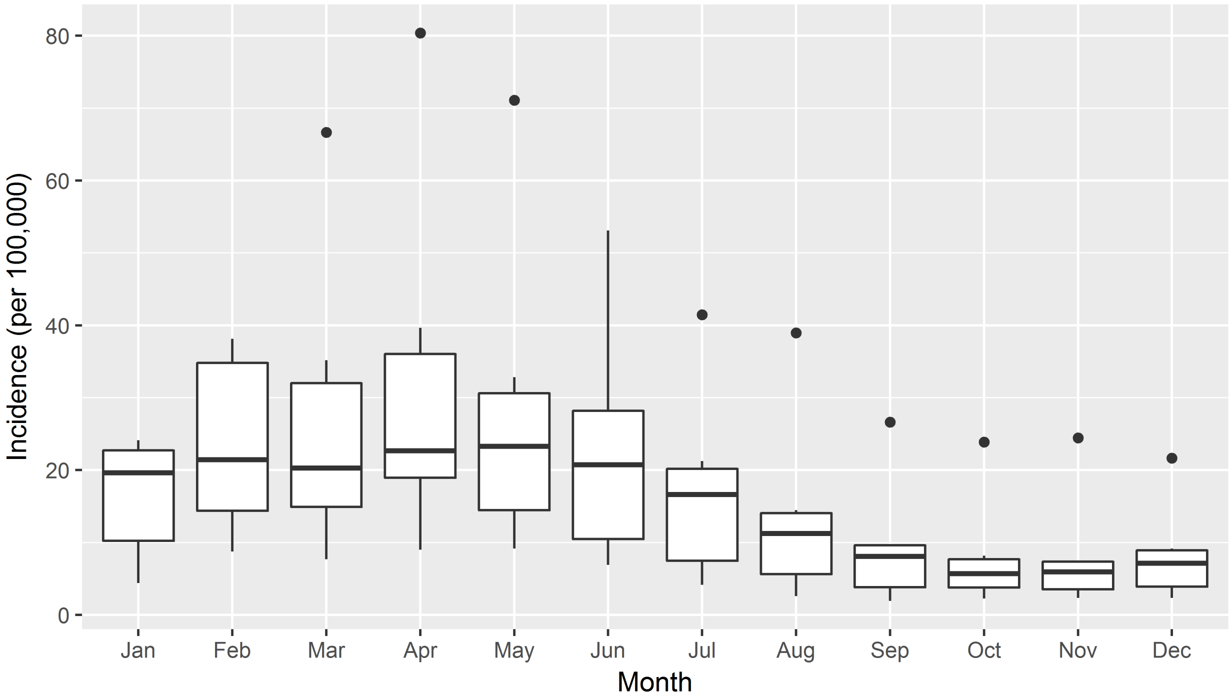
**Fig. 1.** Monthly reported incidence of dengue infection in Bali during 2012-2017. The graph was created using R software (R Development Core Team; 2017, https://www.r-project.org/) with the “ggplot2” package.

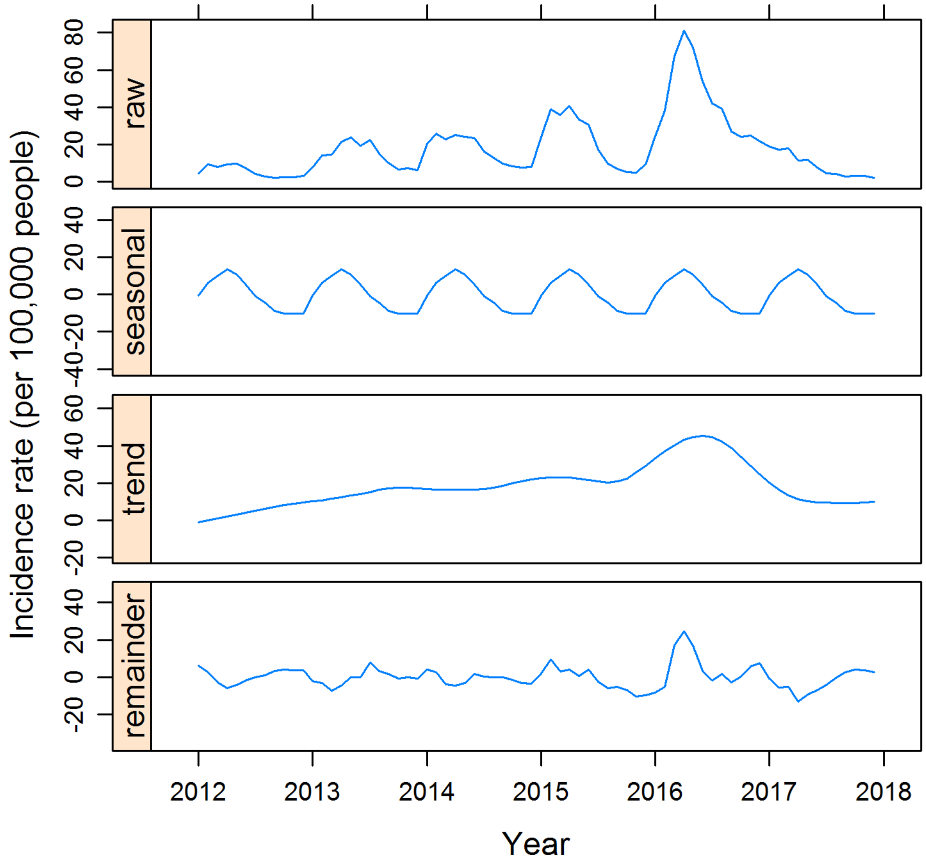
**Fig. 2**. Seasonal trend decomposition plots of notified dengue incidence during 2012-2017. Dengue case clearly shows to have strong seasonality association and reached a peak in the first quarter of the year. Incidence of dengue in Bali showed an increasing trend since 2012, with the highest incidence reported in 2016. The result was generated under R environment (R Development Core Team; 2017, https://www.r-project.org/) using “stlplus” package.

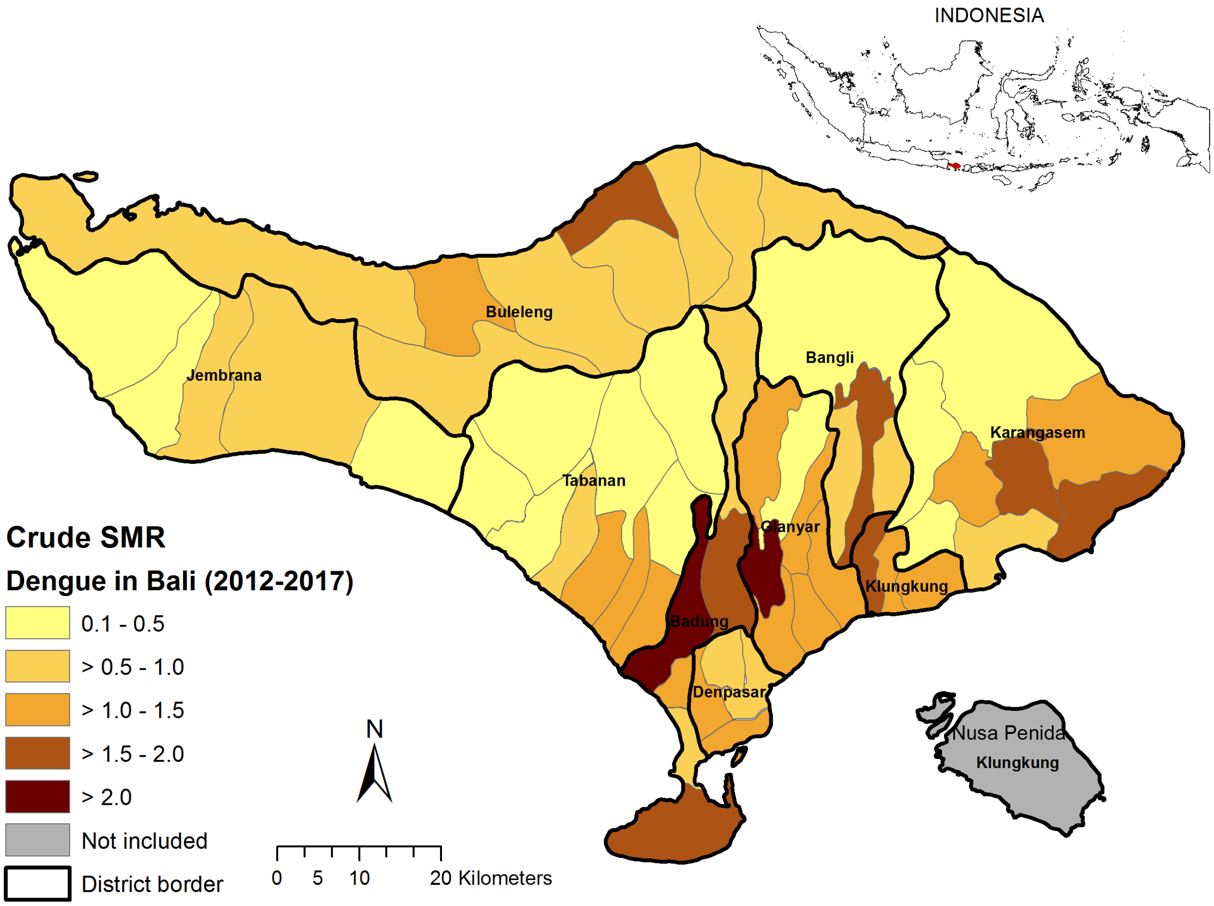
**Fig. 3.** Crude standardized morbidity rates (SMR) for dengue by *kecamatan* in Bali (1 January 2012 to 31 December 2017). The crude rate was spatially clustered in the island, with Mengwi and Ubud having the highest rate among *kecamatans* in Bali. The map was created in ArcGIS 10.5.1 software, ESRI Inc., Redlands, CA, USA, (https://www.arcgis.com/features/index.html).

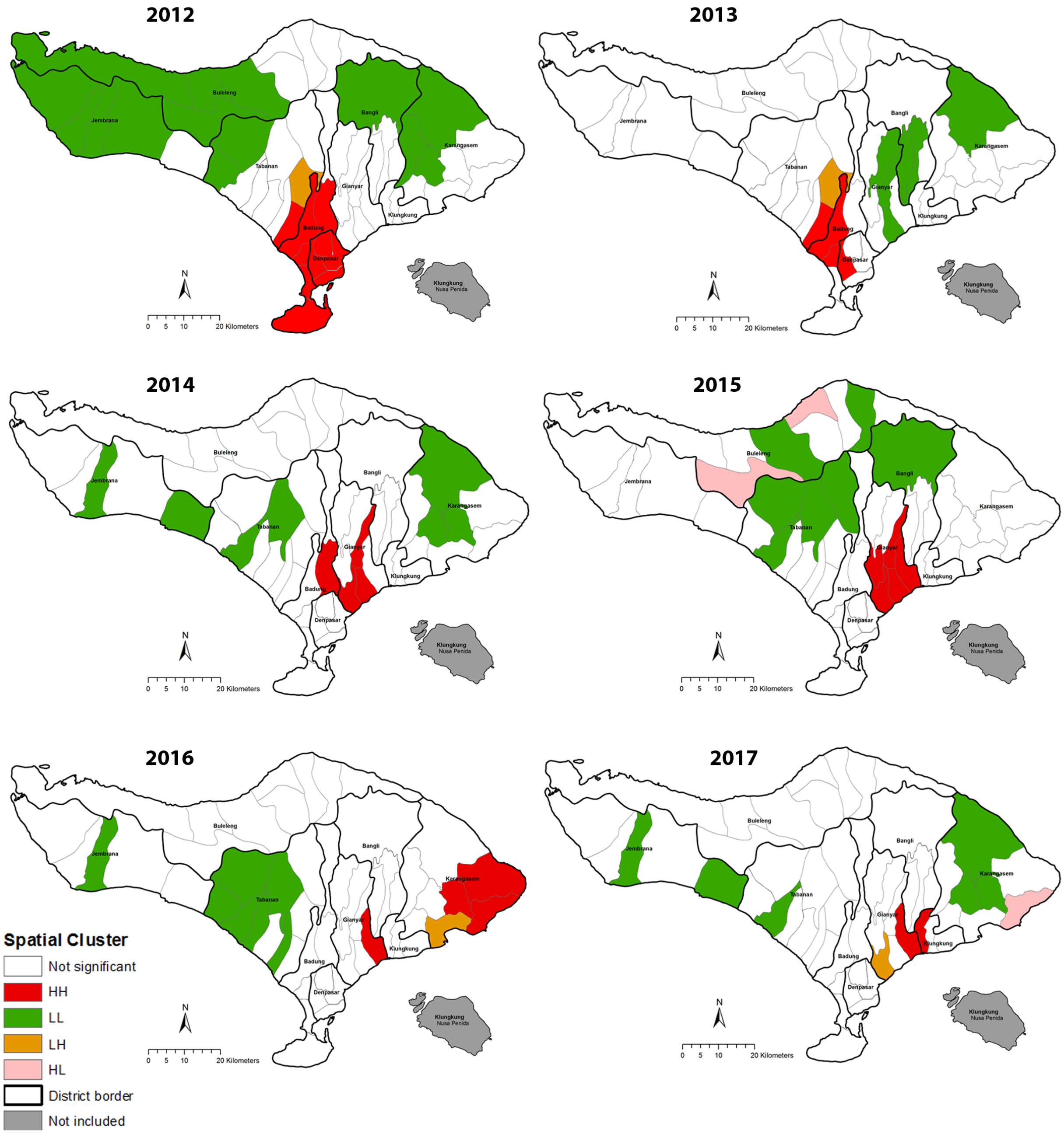
**Fig. 4.** Local indicators of spatial association (LISA) clusters of dengue incidence, Bali island, Indonesia, 2012-2017. The map was created in ArcGIS 10.5.1 software, ESRI Inc., Redlands, CA, USA, (https://www.arcgis.com/features/index.html).

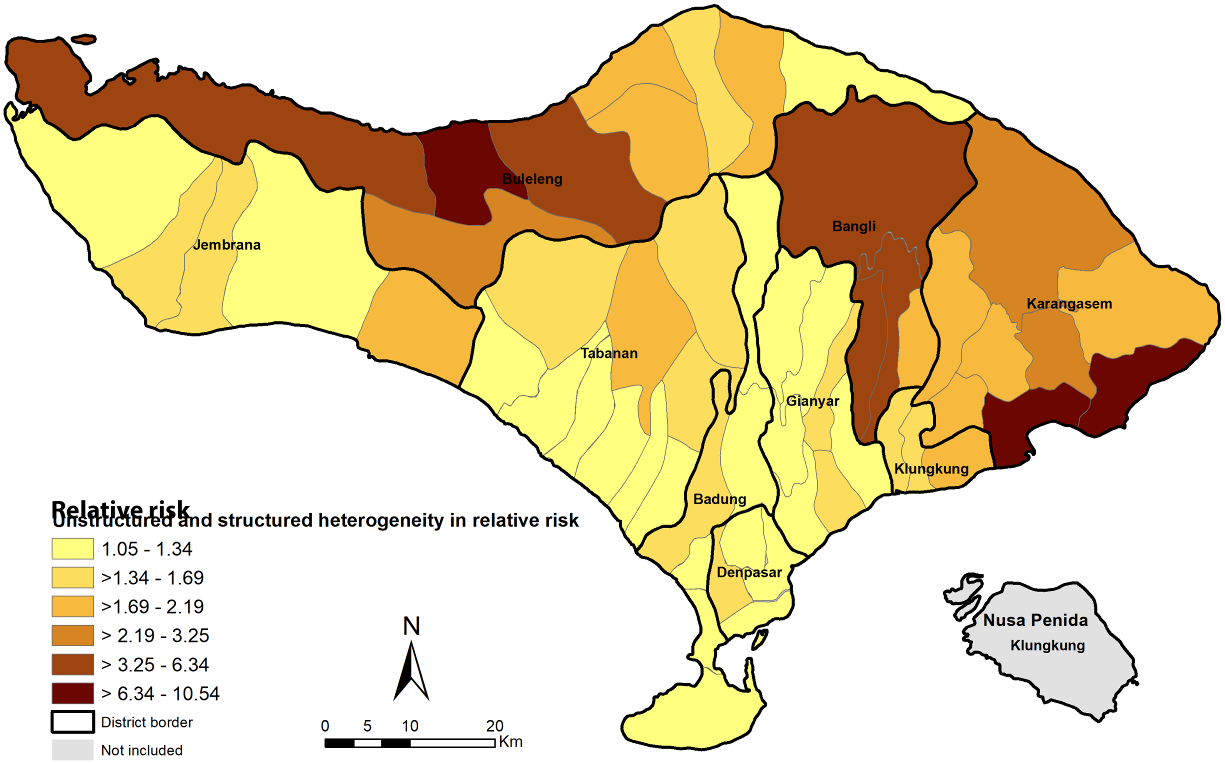
**Fig. 5**. The spatial distribution of posterior mean of the relative risk of fitted model (Model III) for dengue in Bali. The map was created in ArcGIS 10.5.1 software, ESRI Inc., Redlands, CA, USA (https://www.arcgis.com/features/index.html).


Incidence (per 100,000)
80
60
40
20
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Month


raw
seasonal
trend
remainder
Incidence rate (per 100,000 people)
0
20
40
60
80
-40
-20
0
20
40
-20
0
20
40
60
-20
0
20
40
2012
2013
2014
2015
2016
2017
2018
Year


INDONESIA
Buleleng
Jembrana
Bangli
Karangasem
Tabanan
Gianyar
Klungkung
Badung
Denpasar
Nusa Penida
Klungkung
Crude SMR
Dengue in Bali (2012-2017)
0.1 - 0.5
> 0.5 - 1.0
> 1.0 - 1.5
> 1.5 - 2.0
> 2.0
Not included
District border
N
0 5 10 20 Kilometers


2012
Buleleng
Jembrana
Tabanan
Bangli
Karangasem
Gianyar
Klungkung
Badung
Denpasar
Klungkung Nusa Penida
N
0 5 10 20 Kilometers
2013
2014
2015
2016
2017
Spatial Cluster
Not significant
HH
LL
LH
HL
District border
Not included


Buleleng
Jembrana
Bangli
Karangasem
Tabanan
Gianyar
Klungkung
Badung
Denpasar
Nusa Penida
Klungkung
Relative risk
Unstructured and structured heterogeneity in relative risk
1.05 - 1.34
>1.34 - 1.69
>1.69 - 2.19
> 2.19 - 3.25
> 3.25 - 6.34
> 6.34 - 10.54
District border
Not included
N
0
5
10
20
Km