ORIGINAL ARTICLE

Dengue Fever Dynamics in Bali, Indonesia 2010-2018: An Interplay of Population Density and Climatic Factors

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Abstract- Dengue Fever (DF) incidence in Bali has been the highest in Indonesia for decades. This study describes the annual distribution of DF and analyzes its association with population density, number of rainy days, and average humidity during 2010-2018 at the district level. The choropleth maps and Poisson regression were employed to provide geographical distribution and quantify the association. The *P*, 95% confidence interval (CI), and Akaike Information Criterion (AIC) were adopted to assess the significance and the goodness of the association. During 2010-2018 there were 55 215 new DF cases notified. The annual incidence of dengue cases in Bali increased with IRR: 1.000186 (95% CI:1.0000183:1.000189) for every increment of population density per kilometers square and increased by IRR: 1.01043 (95% CI: 1.01019: 1.01078) for every additional one rainy day annually. The dengue cases also increased with IRR 1.0172 (95% CI: 1.0137: 1.0208) for every 1% increase in average humidity. Population density and climate factors are positively associated with dengue cases incidence in Bali from 2010 to 2018. The results underline the urgency of integrating population dynamics and climatic determinants into the DF control program and customizing the intervention program based on local characteristics.

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Keywords: Dengue fever; Bali; Population density; Climatic; Rainy days; Humidity

Introduction

Dengue fever (DF) is a public health threat with rapid transmission worldwide, particularly in the tropical region (1). The disease is found in most Southeast Asia (SEA) countries with an increasing trend in population health burden (2). Indonesia, as DF endemic tropical region, has been significantly impacted by the transmission since the first cases were notified in 1968 only in the two biggest cities of Jakarta and Surabaya. In 2018, all 34 provinces and 85.60% of total districts in Indonesia were affected by this mosquito-borne disease, with a national IR was 24.73 (per 100,000 population) and CFR was 0.70% (3). Bali Province has had rapid DF transmission for decades. The incidence rates (IR) in 2015, 2016, and 2017 were 257.75, 515.9, and 105.95 (per 100,000 population), respectively, which were multiple times above national IRs (50.75, 78.85, and 22.55 per 100000 population) (4).

Bali Island is the top destination for national and international tourism. The Provincial Bureau of Tourism reported total visitors in 2018 were 1.743.474 and 186.436 from domestic and international, respectively. These numbers increased by 248% from the previous year in 2017. Moreover, 184 countries of origins of foreign visitors were recorded by Bali Province Tourism Authority until October 2019 (5). From 2009-to 2010, imported DF cases from Bali were reported in Italy (6) and Japan (7), and it was associated with DF incidence in 5 territories in Australia (8). Moreover, the study of DENV2 in India found the Asian I genotype as one of the circulating variances (9). Thus, DF cases occurring in Bali would threaten national and international health

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security.

The density of the population is one of the driving forces for vector-borne diseases (VBD) incidence as the existence of mosquitoes vectors in the population closely depends on the availability of the hosts (10). The ecological change and increasing population density are also responsible for cross-species transmission (11). While climatic factors have long been studied to play an essential role in DF incidence to provide the favorable biological and ecological conditions for mosquitoes as vectors and dengue virus as an agent (12) and initiates outbreaks in Indonesia (13). Any variability in climatic and weather conditions is a crucial element in projecting the survival and movement of vectors as well as predicting the DF transmission (14).

Regardless of the urgency of DF monitoring in Bali Province to avert any potential threats to global health. It is, however, still limited studies to examine the secondary datasets at a larger scale. The forerunner research analyzed the data for the period 2001-2010, completed with interviews with health officers in Buleleng, Gianyar, and Badung districts (15), while the most recent study analyzed surveillance data from 2012-2017 to quantify climatic and demographic factors (16). This research purposed to continue the previous studies in describing the DF annual case occurrence during 2010-2018 and analyze its association with yearly explanatory variables from demographic factors of population density and climate factors of average humidity and total of rainy days during the observation period. The hypothesis to be examined is there is an association of DF cases number with the socio-demographic factors (population density) and climate factors (average humidity and total of rainy days) during 2010-2018 in Bali Province.

Materials and Methods

Study design and variables

This research used an ecological study design with secondary population datasets at the district level as the unit of analysis. The outcome variable of interest was the number of DF cases in each district. While the explanatory variables were first, the population density was calculated by the number of registered residents of each district divided by the area size (in Kilometer squares). The second was the average humidity, and the third number of rainy days was extracted from the monthly data for each district.

Data source

Dengue fever surveillance datasets 2010-2018 were extracted from provincial and districts' health profiles. The data was validated by confirmation with the latest report from the Bali Province health office. The demographic data on population density was extracted from the Indonesian Bureau of Statistics (BPS). The climatic data of average humidity and the number of rainy days were obtained directly from the Bureau of Meteorology, Climatology, and Geophysics (BMKG) office in Bali Province. Classification based on climatic zone was used to determine the climate datasets in each district.

Data analysis

The choropleth maps were generated for each consecutive 9 years to see the geographical pattern of IR, population density, average humidity, and the number of rainy days. The 4 layers were overlaid to visually describe the pattern of DF incidence rates and explanatory variables simultaneously. Categorization of values was based on normal classification. The maps were generated using ArcMap/ArcGIS 10.4 by ESRI.

A statistical test was employed to examine the geographical structure of DF IR values dependency distribution. This detection examines whether the adjacent IRs values are distributed randomly, clustered, or dispersed throughout Bali Province. Global Moran, I autocorrelation is formulated as below:

$$I = n\sum_i\sum_j W_{ij}C_{ij}/\sum_i\sum_j W_{ij}\sum_i(Z_i-\overline{Z})^2$$

n = the number of districts in Bali province

i, j = any of two districts

Z_i = the IR value of district *i*

C_{ij} = the similarity of IR values of district *i* and *j*

W_{ij} = the similarity of locations of districts *i* and *j*

$(Z_i-\overline{Z})^2$ = the difference of IR values between two districts compared with average IRs

This analysis was performed by using ArcGIS/ArcMap 10.4 software certified by ESRI.

The preliminary analysis of univariate Poisson regression was conducted to select the variables to be included in the model and examine the association of DF case numbers with every single explanatory variable. The P<0.05, 95% confidence interval (CI), and Akaike Information Criterion (AIC) was employed to assess the significance of the association. The missing data from incomplete reported datasets was handled using the imputation mean of neighboring values. The analysis was performed using STATA 14 by Stata Corp, College Station, Texas, USA.

The number of dengue fever cases occurrence is assumed to follow Poisson distribution under frequentist statistics as below:

$$\theta_{ii} \sim Poisson\ (\mu_{ij})$$
$$Log\ \theta_{ij} = \alpha + (\beta_1\ x\ pop\ density_{ij}) + (\beta_2\ x\ average\ humidity_{ij}) + (\beta_3\ x\ number\ of\ rainy\ days_{ij})$$

$\theta_{i\,j}$ is the number of DF cases in Bali Province in year i, and district j, while α is the intercept, β_1, β_2, and β_3 are the coefficients for the three independent variables (population density, average humidity, and the number of rainy days).

The goodness of fit of the model is examined by looking at the P<0.05, 95% Confidence Interval (CI), Akaike Information Criterion (AIC) and Deviance goodness of fit, and Pearson goodness of fit. The analysis was performed using STATA 14 by Stata Corp, College Station, Texas, USA.

Ethical clearance

These research protocols have been approved by the Health Research Ethics Committee, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia, with reference number: No.208/EA/KEPK/2019 on October 1st, 2019.

Results

Descriptive frequency distribution and choropleth mapping

During 9 observed years from 2010-to 2018, there were 55,215 new DF cases notified by Bali Provincial Health Office for the entire Islands. The smallest number of cases was 19, and the highest was 4199 (median 847.95 cases). The IR range was 4.58-786.33 per 100000 population (with a median value of 194.30). The density of the population varied from 312-to 7,283 per kilometer squares (with a median value of 1,367.84). The climate determinants of the rainy days range from 100-to 239 (with a median value of 153.44) per year, while the average humidity ranges from 71.58-to 86.67 (with a median value of 80.29) (Table 1).

The DF IR reached its peaks in 2015 and 2016, where the IRs for the entire nine districts in Bali were above 125/100000 population and above 200/100000 population, respectively. The choropleth maps of IR were darker as the density dots for population and rainy days were more rapid. Inversely, the IR values were darker as the circles of average humidity were smaller.

The districts impacted by DF were changing over time, whereas in 2010, Denpasar, Badung, and Buleleng were positioned as the highest IRs. Denpasar, Badung, and Gianyar are frequently positioned as the most impacted by DF transmission. In 2018, it was Klungkung the highest, followed by Badung and Buleleng (Figure 1, 2).

Aside from the values of the dynamic throughout 9 years, Denpasar and Badung consistently had IR above 100/100000 population until 2017; only after 2018 did their IRs decrease. The population density in Denpasar was the highest during 9 years of observation, where the density minimum in 2010 amounted to 6206 population/ kilometer square and reached its peak in 2018 in the amount of 7282.83 population/ kilometer square. Jembrana has the consistent lowest population density ranging from 312 population/kilometer square in 2010 to 328.58 population/ kilometer square in 2018 (Supplement 1).

Buleleng was the district with total rainy days always the highest each year from 2010 (239 days) until 2018 (155 days). Buleleng was also recorded as the most humid region in Bali Province, the maximum humidity was in 2018 (86.67%), and the minimum was in 2014 (82.25%). While Tabanan and Bangli were frequently positioned as the districts with the lowest total rainy days throughout 9 years of observation. In 2015, it was recorded as the driest year, where total rainy days in Tabanan and Bangli were 103 and 107, respectively (Supplement 2).

Global moran I

The result of the Global Moran I test suggested that the significant cluster autocorrelation was only detected in 2012 (The Global Moran I index value=0.330654, P 0.019985). 2010, 2011, 2013, 2014, 2016 showed positive Moran I index values; however, it did not show any spatial statistics significance as the P>0.1. While 2015, 2017, and 2018 have negative Moran, I index values (Supplement 4).

Univariate analysis of Poisson regression

The three explanatory variables (population density, number of rainy days, and average humidity) were significantly associated with yearly DF cases number in Bali Province. The result of the multicollinearity test after multiple regression showed that all of the variables have a variance inflation factor (VIF) below 4. It indicated there was no multicollinearity among these variables (Supplement 3).

Multivariate non spatial Poisson regression model

All of the explanatory variables included in the model were significantly and positively associated with the number of DF cases in Bali Province. The DF case Incidence Rates Ratio (IRR) was elevated by 1.000186 (95% CI: 1.0000183 : 1.000189) for every increment of population density per kilometers square and increased by IRR: 1.01043 (95% CI: 1.01019: 1.01078) for every additional one rainy day annually. The dengue cases also increased with IRR 1.0172 (95% CI: 1.0137: 1.0208) for every 1% increase in average humidity (Table 2).

Table 1. Descriptive Frequency Distribution of Yearly Variables and Covariates 2010-2018

Variables and covariates	Median	Min	Max
Number of Cases	847.95	19	4199
Population Density	1,367.84	312	7,283
Number of Rainy Days	153.44	100	239
Average Humidity	80.29	71.58	86.67
Case Fatality Rates (CFR)	0.148	0	1.2
Incidence Rates (IR)	194.30	4.58	786.33
Population Number	445,960	175,430	930,619
Mortality Number	1.91	0	24

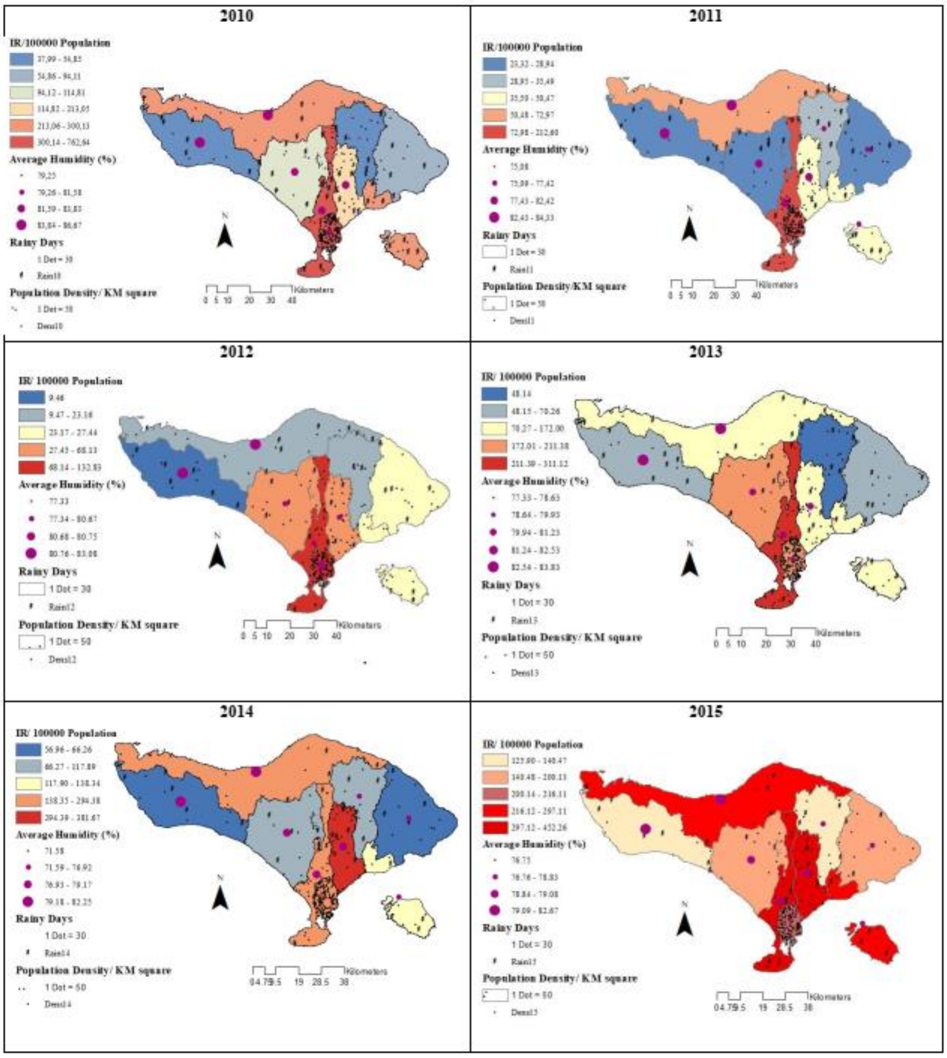

Figure 1. Geographical Distribution of Yearly Incidence Rates (IR), Population Density, Average Humidity, and Number of Rainy Days 2010 – 2015 in Bali Province

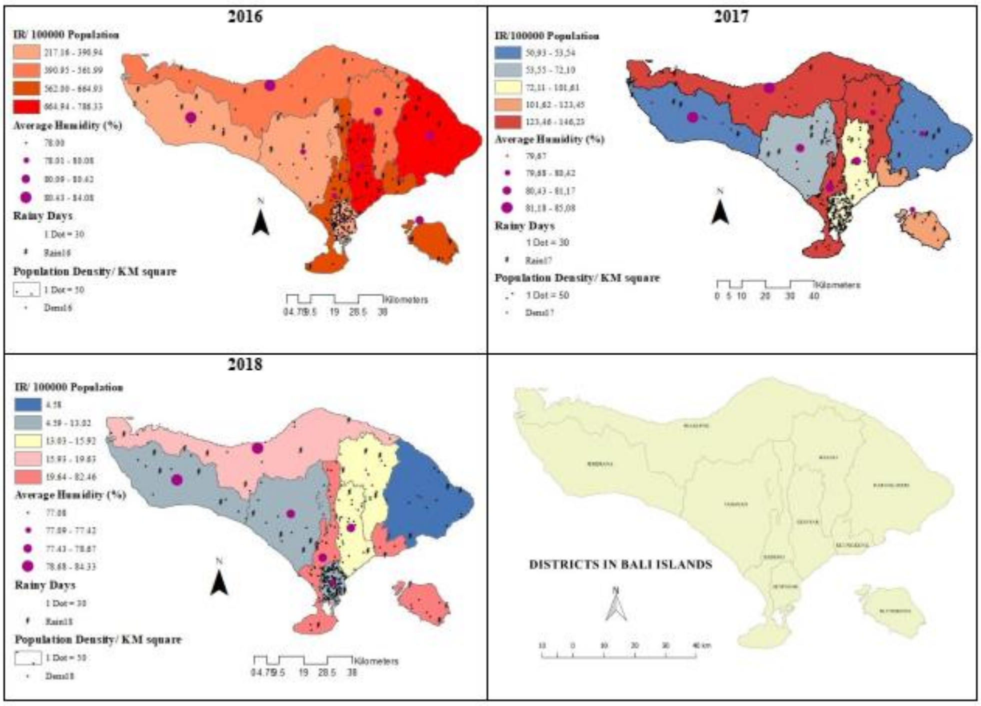

Figure 2. Geographical Distribution of Yearly Incidence Rates (IR), Population Density, Average Humidity, and Number of Rainy Days 2016 – 2018 in Bali Province

Table 2. The Results of Multi-variates Analysis with Multiple Poisson Regression of DF Case Number with All Explanatory Variables (Population Density, Number of Rainy Days, and Average Humidity) in Bali Province 2010-2018

Variables	IRR	95% CI	*P*
Constant	29.919	23.158:38.655	0.000
Population Density*	1.000186	1.000183:1.000189	0.000
Number of Rainy Days*	1.01043	1.01019:1.01078	0.000
Average Humidity*	1.0172	1.0137:1.0208	0.000

*statistically significant

Discussion

The trend of DF incidence in Bali Province increased from 2010-to 2016 and sloped down from 2017-to 2018. Denpasar and Badung were the districts with the highest intensity of DF transmission. This study linear with the previous findings that 2016 was recorded as the heaviest transmission in Bali Province (16). El Nino Southern Oscillation (ENSO) by the end of 2015, followed by the La Nina 2016 event, could be the underlying condition that brought the high intensity of rainfall (17).

Each of the nine districts in Bali Province has its own characteristics. Denpasar and Badung are the districts with the highest population density as recorded in 9 years of observation. The pattern of the high population density of both districts has coincided with the high IRs in most of the observed years. This condition is linear with a previous study of the 2014-2015 outbreak in Taiwan that the population density gradient of urban and suburban along with population mobility are significant predictors of the dengue epidemic (18). Moreover, both districts were reported as the most visited destination until 2019 (5) hence it is most likely that population mobility is also high in both areas regardless of their area size. The geographical feature of Buleleng is closer to equators; therefore, the tropical climate characteristics are more profound. On the other side, Klungkung, Gianyar, and Tabanan locations are varied from northern parts that are dominated by hills and mountains while the southern parts are coastal areas.

The cluster autocorrelation was found in 2012, which is similar to the previous study; however, the discrepancy was indicated as a study in 2019 used sub-district as the unit of analysis (16), while this study used district as the unit of analysis. These findings highlight how different geographical aggregation scale analyses would result in a different result, known as modifiable area unit problem (MAUP) (19), at the same time indicating the limitation of the present datasets .

The Population density is positively associated with DF cases occurrence in Bali Province. This condition might be indirectly driven by the blood-feeding plasticity behavior of mosquitos vectors, that the availability of the human host is responsible for the interaction rather than the vector preference (10). During the 2004-2005 Singapore DF epidemics, human population growth was reported to contribute to exacerbating the transmission (20). The same findings for DF case in the overpopulated area of Bangladesh (21).

Even though another experimental research in Japan found that the decrease in hosts availability was correlated with bite rates (22), this study also highlighted the role of hots availability in predicting the outbreak with the complex relationship of secondary infection (22). Aedes Aegypti mosquitos, vectors for DF characterized as anthropophilic that is rely on human existence (11,23). Human is indicated as one of the amplification hosts for the dengue virus, where the dengue virus replication occurs highly intensive to transmit to other host (11).

The DF case number is positively associated with the number of rainy days. These findings agreed with previous research in Sri Lanka that found a positive association of DF incidence 2003-2012 with various climate variables (rainfall, number of rainy and wet days, temperature, night and day time, and average humidity) within 5-7 weeks-time lag (24). Even though the unit of analysis of this study was yearly. Thus, the analysis was performed without time lags .

These results are slightly different from previous research in Bangladesh in 2016, in which, at certain rainfall intensity (>15 mm), the dengue transmission would decrease (25). In the meanwhile, a recent study in 2019 emphasized that climate factors, including rainfall as the profound determinants of DF in Bali (8). A study in China (2017) also stated that rainfall takes the role of the indirect determinant for DF incidence mediated by the density of vectorsm (26). The findings are consistent with the study in Puerto Rico (2014) that the annual number of days with precipitation>10 mm/ 24 hours could elevate transmission intensity (27).

The average humidity during nine observed years was positively associated with the DF case occurrence number in 9 districts in Bali Province. The different phenomena were captured in the sub-tropical region of Brazil that found a negative association between humidity and vector population (28). On the other side, a study from Sri Lanka reported a similar result with Bali, a positive association between average humidity and dengue fever incidence (24). This discrepancy result might be driven by different parameters, whereas in Bali and Sri Lanka, the observed variables were average humidity and DF occurrence. Meanwhile, a study in Brazil used vector population as a proxy of the outcome, and Vietnam research used total hours of sunshine as the explanatory variable.

Aside from its wide coverage of time units observed, there are some areas of improvement in this research. First, the analysis of the unit used was at the district level, and yearly that it is challenging to derive causation inference at a lower scale due to ecological fallacy. Second, the validation of surveillance data process quality was not confirmed. Nevertheless, this study could comprehend the current discussion concerning DF distribution in the most visited tourist area. In brief, the intervention program for DF monitoring, controlling, and prevention need to be customized for each district based on their local characteristics in order to avoid any outbreak. Further study at a finer unit analysis scale is highly recommended to provide comprehensive results and recommendations.

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The authors sincerely thank to Bali Province Health Office and Meteorology, Climatology and Geophysics Bureau (BMKG) for providing the datasets.

Supplement 1. Descriptive Frequency Distribution of Incidence Rates (IR) and Social Factor of Population Density in Bali Province 2010-2018

Kabupaten	2010		2011		2012		2013		2014	
	IR	Density	IR	Density	IR	Density	IR	Density	IR	Density
Buleleng	300.13	459.00	72.97	462.00	19.11	494.56	155.73	467.32	254.77	470.25
Jembrana	37.99	312.00	23.32	314.00	9.46	326.38	63.69	318.37	56.96	320.50
Tabanan	114.81	417.00	26.08	419.00	68.13	525.33	187.59	513.03	112.37	516.25
Badung	755.07	1306.00	212.60	1340.00	118.78	1383.9	311.12	1407.34	294.38	1440.07
Denpasar	762.64	6206.00	180.17	6346.00	132.83	6632.5	211.38	6622.32	217.72	6758.49
Gianyar	213.05	1282.00	50.47	1295.00	61.31	1380.8	172.00	1320.65	381.67	1332.88
Bangli	54.85	440.00	35.49	443.00	23.16	422.8	48.14	422.42	117.89	424.92
Klungkung	285.01	543.00	47.31	546.00	26.99	592.03	142.64	552.06	138.34	554.92
Karangasem	94.11	474.00	28.94	476.00	27.44	482.53	70.26	481.57	66.26	484.31
Kabupaten	**2015**		**2016**		**2017**		**2018**			
	IR	**Density**	**IR**	**Density**	**IR**	**Density**	**IR**	**Density**		
Buleleng	297.11	473.10	560.61	475.96	136.17	478.52	19.63	481.16		
Jembrana	125.90	322.64	311.30	324.66	50.93	326.56	13.02	328.58		
Tabanan	200.13	519.34	217.16	522.44	72.10	525.42	9.92	528.40		
Badung	362.24	1472.81	664.93	1505.30	146.23	1537.56	55.71	1569.58	--	--
Denpasar	216.11	6891.53	390.94	7022.23	101.61	7155.27	12.25	7282.83		
Gianyar	452.26	1345.38	785.36	1357.61	101.41	1369.29	14.17	1380.71		
Bangli	140.47	427.41	561.99	429.72	142.16	432.21	15.92	434.32		
Klungkung	258.01	557.78	629.48	560.95	123.45	563.17	82.46	566.03		
Karangasem	193.30	486.81	786.33	489.32	53.54	491.70	4.58	494.08		

Supplement 2. Descriptive Frequency Distribution of Incidence Rates (IR) and Climatic Factor of Number of Rainy Days and Average Relative Humidity in Bali Province 2010-2018

Kabupaten	2010			2011			2012			2013			2014		
	IR	Rain	Humid	IR	Rain	Humid	IR	Rain	Humid	IR	Rain	Humid	IR	Rain	Humid
Buleleng	300.13	239	86.67	72.97	188	84.33	19.11	166	83.08	155.73	197	83.83	254.77	149	82.25
Jembrana	37.99	239	86.67	23.32	188	84.33	9.46	166	83.08	63.69	197	83.83	56.96	149	82.25
Tabanan	114.81	189	83.83	26.08	174	82.42	68.13	137	80.67	187.59	167	80.42	112.37	115	79.17
Badung	755.07	189	83.83	212.60	174	82.42	118.78	131	80.67	311.12	157	80.42	294.38	160	79.17
Denpasar	762.64	199	81.58	180.17	170	75.08	132.83	133	80.75	211.38	155	78.83	217.72	121	71.58
Gianyar	213.05	189	83.83	50.47	174	82.42	61.31	131	80.67	172.00	157	80.42	381.67	160	79.17
Bangli	54.85	189	79.25	35.49	174	77.42	23.16	134	77.33	48.14	136	77.33	117.89	118	76.92
Klungkung	285.01	199	79.25	47.31	170	77.42	26.99	133	77.33	142.64	155	77.33	138.34	121	76.92
Karangasem	94.11	193	79.25	28.94	141	77.42	27.44	118	77.33	70.26	176	77.33	66.26	119	76.92
Kabupaten	**2015**			**2016**			**2017**			**2018**			--	--	--
	IR	**Rain**	**Humid**	**IR**	**Rain**	**Humid**	**IR**	**Rain**	**Humid**	**IR**	**Rain**	**Humid**	--	--	--
Buleleng	297.11	143	82.67	560.61	218	84.08	136.17	130	85.08	19.63	155	84.33	--	--	--
Jembrana	125.90	143	82.67	311.30	218	84.08	50.93	178	85.08	13.02	155	84.33	--	--	--
Tabanan	200.13	103	79.08	217.16	173	80.08	72.10	142	81.17	9.92	112	78.67	--	--	--
Badung	362.24	124	79.08	664.93	183	80.08	146.23	145	81.17	55.71	100	78.67	--	--	--
Denpasar	216.11	111	76.75	390.94	156	78.00	101.61	141	79.67	12.25	110	77.42	--	--	--
Gianyar	452.26	124	79.08	785.36	183	80.08	101.41	145	81.17	14.17	100	78.67	--	--	--
Bangli	140.47	107	78.83	561.99	153	80.42	142.16	141	80.42	15.92	130	77.08			
Klungkung	258.01	111	78.83	629.48	156	80.42	123.45	141	80.42	82.46	110	77.08			
Karangasem	193.30	116	78.83	786.33	160	80.42	53.54	157	80.42	4.58	119	77.08			

Note:
IR : Incidence Rates per 100,000 Population
Density: Population density (number of residents per kilometer square of administrative area)
Rain: Number of rainy days per year (days)
Humid: Average humidity per year (%)

Supplement 3. The results of Uni-Variate analysis of Poisson Regression of case number with each of explanatory variables (population density, number of rainy days and average humidity)

Variables	IRR	95% CI	*P*	VIF
Population Density	1.000002	1.000002:1.000002	0.000	1.13
Number of Rainy Days	1.008975	1.008751 :1.009198	0.000	1.61
Average Humidity	1.03607	1.033327 :1.03882	0.000	1.77

Supplement 4. The Result of Moran I Test for Each Year to Detect Autocorrelation or Cluster in Bali Province 2010-2018

Year	Moran's Index	Z Score	Variance	*P*
2010	0.144206	1.402867	0.036825	0.160656
2011	0.158101	1.539830	0,033802	0.123602
2012*	0.330654	2.326629	0.038354	0.019985*
2013	0.126071	1.331231	0.035570	0.183113
2014	0.042597	0.847887	0.039071	0.396501
2015	-0.149305	-0.128276	0.035901	0.897930
2016	0.134838	1.295253	0.195233	0.195233
2017	-0.148262	-0.112865	0.042480	0.910138
2018	-0.315876	-1.146561	0.027714	0.251563

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