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ORIGINAL RESEARCH

Estimating Effects of Temperature on Dengue Transmission in Colombian Cities

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Abstract

BACKGROUND Dengue fever is a viral disease that affects tropical and subtropical regions of the world. It is well known that processes related to virus transmission by mosquitoes are highly influenced by weather. Temperature has been described as one of the climatic variables that largely governs the development and survival of mosquito eggs as well as the survival of all insect stages. Previously, we noted that high temperatures in the Colombian city of Riohacha negatively affect the establishment of dengue virus (DENV) infection in mosquitoes; in Bello and Villavicencio cities, which have lower average temperatures, DENV infection rates in mosquitoes are positively associated with a gradual increase in temperature. Here, we test the hypothesis that a similar effect of temperature can be detected in the incidence in the human population inhabiting dengue-endemic cities in Colombia.

OBJECTIVE Our objective was to evaluate the effect of climate variables related to temperature on DENV incidence in human populations living in DENV-endemic cities in Colombia.

METHODS Epidemiologic data from the Instituto Nacional de Salud from 2012-2015 and 7 variables related to temperature were used to perform Spearman rank sum test analyses on 20 Colombian cities. Additionally, locally estimated scatterplot smoothing analyses were performed to describe the relationship among temperatures and incidence.

FINDINGS Results indicated that Colombian cities with average and maximum temperatures greater than 28°C and 32°C, respectively, had an inversely related relationship to DENV incidence, which is in accordance with areas where higher temperatures are recorded in Colombia.

CONCLUSION Climatic variables related to temperature affect dengue epidemiology in different way. According to the temperature of each city, transmission might be positively or negatively affected.

KEY WORDS climatic variables, correlation analysis, correlation coefficient, dengue, incidence, temperature.

INTRODUCTION

Dengue fever is a viral disease present in tropical and subtropical regions of the world. It is estimated that around 390 million infections occur each year, but only about 96 million people manifest the infection clinically.[1] The virus is transmitted by mosquitoes belonging to *Aedes* genus, of which the most important species is *Aedes aegypti* because of its high anthropophily.[2,3] Once the mosquito feeds on a viremic human, the virus establishes the infection in the midgut of the insect, where it then disseminates (or not) from the midgut to other tissues, including the salivary glands. Those mosquitoes that do allow virus

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infection, replication, dissemination, and ultimately transmission of the virus are known as competent vectors of the virus.[4]

It is well known that processes related to virus transmission are influenced by weather. Numerous associations between different climatic variables and dengue cases have been broadly described (as reviewed by Morin et al[5]). However, temperature is one of the most studied variables and has been described as the climatic variable that largely governs the development and survival of mosquito eggs as well as the survival of all stages of the insect.[6,7] Results of these studies lend evidence to the idea that the optimal temperature for mosquito development at all stages ranges from approximately 20°C-30°C.[8-10]

In addition to mosquito life traits, temperature affects the course of infection within the mosquito, and it has been noted that an increase of temperature leads to a reduction in the extrinsic incubation period.[11] Moreover, overall dengue virus (DENV) infection proportions in mosquitoes are believed to be influenced by low and high temperatures.[12] Recently it was reported that daily fluctuations of low and high temperatures have a significant effect on development and DENV infection rates of mosquitoes, where large temperature fluctuations are correlated with slower mosquito development and low infection rates,[13-16] but such fluctuations at low mean temperature accelerate DENV transmission by mosquito.[17]

Based on this, a large amount of evidence supports a relationship between temperature and dengue incidence in human populations (as reviewed by Morin et al,[5] Naish et al,[18] and Junxiong and Yee-Sin[19]). Fan et al[20] developed a meta-analysis indicating an increase in the risk of dengue fever through an increase in temperature, where mean temperature was found to be more important than maximum and minimum temperatures. Interestingly, from 29°C the odds ratio of dengue risk began to decline,[20] suggesting a nonlinear effect of temperature.

In agreement with this, we recently reported that temperature differentially affects the DENV infection of mosquitoes in 3 Colombian cities.[21] We found that high temperatures in the city of Riohacha negatively affected infection by DENV, whereas in Bello and Villavicencio municipalities, which have lower average temperatures, DENV infection rates in mosquitoes were positively associated with a gradual increase in temperature.[21] As with any mosquito-borne virus, infection rates in the mosquito population are necessarily tied to transmission to the human population. Thus, we wished to determine if temperature-related variables correlated to dengue incidence patterns, so we investigated the correlation between climatic variables related to temperature of 20 Colombian cities and dengue incidence of those cities. Our aim was to describe a general pattern in dengue incidence and temperature that can be further applied at the national level to develop a temperature-stratified risk map of Colombia to improve disease control strategies and make better use of resources. With this in mind, we developed a model of temperature behavior through a range of temperature values to be applied to different regions of Colombia.

MATERIALS AND METHODS

Epidemiologic Data. We collected epidemiologic data about dengue cases from 20 Colombian cities that are available from the Colombian National Institute of Health (Instituto Nacional de Salud [INS] in Spanish) website (http://www.ins.gov.co/lineas-de-accion/Subdireccion-Vigilancia/sivigila/Paginas/vigilancia-rutinaria.aspx) from January 2012 to December 2015. These cities were selected because of continuous reports of dengue cases, altitudinal range (between 0 and 1457 m above sea level), population size (<1 million) and different ranges of temperature (Table 1).

Climatic Data. Daily climatic data were acquired from the Instituto de Hidrología, Meteorología y Estudios Ambientales (IDEAM) of Colombia (www.ideam.gov.co), the Colombian public institution of technical and scientific support to the national environmental systems. Climatic data were acquired for the same time frame as the epidemiologic data. Data included variables related to temperature as follows: average temperature (TEMP-AVER), maximum absolute temperature (TEMP-MAXABS), minimum absolute temperature (TEMP-MINABS), average of maximum temperatures (TEMP-AVERMAX), average of minimum temperatures (TEMP-AVERMIN), maximum difference of daily temperatures (TEMP-MAXDIF), and averaged daily temperatures difference (TEMP-AVERDIF).

Statistical Analyses.

Relationship between Climatic Variables and Epidemiologic Patterns in Each City. To examine variability in epidemiologic and climatic data over different time intervals, we conducted analyses between incidence and the 7 climate variables at different lag times. Specifically, we conducted Spearman analyses at (1) 1-week intervals beginning with the current week of incidence and the previous 8 weeks

Table 1. Cities Used in This Study and Their Main Characteristics

City	Projected population in 2012*	Estimated Dengue Incidence in 2012 (per 100,000 population)†	Average Temperature (°C)‡	Altitude (MASL)
Apartadó§	162,914	52.78858784	27.61	30
Barrancabermeja	191,718	262.886114	28.65	84
Bello‖	429,984	28.83828235	22.74	1457
Buenaventura§	377,014	18.30170763	25.72	9
Florencia	163,323	277.3644863	25.93	271
Magangué	123,312	162.1902167	28.48	23
Neiva	335,578	680.3187336	28.35	480
Palmira	298,667	14.73212642	23.92	1012
Pereira	462,230	25.96110162	22.22	1373
Quibdó§	115,054	18.25229892	26.61	47
Riohacha‖	231,641	36.26301043	28.87	8
San José del Guaviare	61,383	105.892511	25.92	185
Santa Marta	461,810	47.85517854	28.93	19
Sincelejo	263,751	222.1792524	27.32	212
Soledad	566,592	39.534621	28.03	45
Tuluá§	204,125	46.54011023	23.46	974
Tumaco	187,084	31.53663595	26.36	4
Valledupar	423,260	207.2012475	29.25	172
Villavicencio‖	452,472	463.4540922	26.24	446
Yopal	129,938	431.7443704	27.3	333

MASL, meters above sea level.
* Projection made by Departmento Administrativo Nacional de Estadística.
† Estimated using projected population in 2012 and total dengue cases reported for the city for 2012 by Instituto Nacional de Salud.
‡ Data subtracted from daily averages from 2012-2015 provided by Instituto de Hidrología, Meteorología y Estudios Ambientales.
§ Municipalities excluded from locally estimated scatterplot smoothing analysis because of presumable underreporting dengue cases.
‖ Municipalities originally studied in previous work.[21]

(9 total analyses) and (2) 2-week intervals beginning with the current week and the previous 12 weeks (7 total analyses). In total, we performed 16 correlation analyses between dengue incidence and the 7 climatic variables per city. The goal of investigating these 2 lag times was to determine the role of lag time in processes on incidence.

To understand whether each climatic variable was positively or negatively related to dengue cases, Spearman correlation coefficients (ρ) from each variable for each city at all lagged times were plotted together and examined for significant and whether those correlations were positive or negative. The relative importance of each variable in each city was based on the number of significant correlations with dengue cases at a confidence level of 95%. Therefore, we considered that a variable was more important as the number of significant correlations increased.

Statistical analyses were carried out using the R Software Version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria). Data management was done with Microsoft Excel 10 (Microsoft Corp., Redmond, WA), and graphs were plotted using GraphPad Prism 5 (GraphPad Software Inc., La Jolla, CA).

General Patterns of Incidence and Temperature. We performed analyses of local regression (locally estimated scatterplot smoothing [LOESS]) to evaluate the relationship between dengue incidence and temperature (minimum, medium, and maximum) by using data from 16 of 20 cities used in this study. Four cities were excluded from this analysis because of lack of or few significant correlations. The cities and the number of correlations found to be significant are indicated in Table 1.

Because epidemiologic data from INS is given by epidemiologic week, we estimated the weekly incidence of dengue during the study time using data of projected growth population estimated by the National Administrative Department of Statistics (Departmento Administrativo Nacional de Estadística) for 2005-2020 (https://www.dane.gov.co/index.php/estadisticas-por-tema/demografia-y-poblacion/proyecciones-de-poblacion). We then used the estimated average weekly dengue incidence of the study cities to perform the LOESS analyses. We

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extracted the average minimum, medium, and maximum temperature to perform a LOESS analysis for each temperature by using data from the cities jointly. Analyses were carried out in R software using the function ggplot from the package ggplot2.

RESULTS

Our results indicate that the most important variables with respect to the number of significant correlations were as follows (in order of most to least importance): TEMP-AVER, TEMP-MAXABS, TEMP-AVERMAX, TEMP-AVERMIN, TEMP-AVERDIF, TEMP-MINABS and lastly TEMP-MAXDIF (Table 2). Results related to correlations between dengue cases and temperature indicated that cities were grouped in 3 effect types (Fig. 1). In the first group, temperature exerted a negative effect on dengue cases. This group was composed of the cities Riohacha, Santa Marta, Valledupar, Neiva, Barrancabermeja, Magangué, Soledad, and Sincelejo. In the second group (composed of Tumaco, Palmira, Florencia, Yopal, Pereira, San José del Guaviare, Bello, and Villavicencio), temperature was positively associated with dengue cases. In the third group (composed of Buenaventura, Tuluá, Apartadó, and Quibdó), there were few or nonsignificant correlations, making it difficult to define the role of temperature on dengue cases in those cities (Fig. 1). The distribution of temperature values revealed that the cities with the highest temperatures were those with negative correlations between temperature and dengue cases (red boxes in Figs. 1 and 2). Cities with lower temperatures similar to Bello or Villavicencio had positive correlations with number of dengue cases (green boxes in Figs. 1 and 2).

The cities belonging to first group (negative correlations) are located in northern Colombia and throughout the middle of the eastern and central Colombian mountain ranges, in the Magdalena river basin (Fig. 3). The second group, composed by cities with positive correlations, is mainly located at the center (excluding the Magdalena river basin) and southwest of Colombia. On the other hand, cities belonging to third group (lack of association) are located in western Colombia (Fig. 3).

Finally, the LOESS analyses identified an increase of dengue incidence with an increase of

Table 2. Number of Significant Correlations (95% confidence) Among Climatic Variables Related to Temperature and Dengue Cases in 20 Colombian Cities During 2012 and 2015

City	TEMP-AVER	TEMP-MAXABS	TEMP-MINABS	TEMP-AVERMAX	TEMP-AVERMIN	TEMP-MAXDIF	TEMP-AVERDIF	TOTAL
Apartadó	1	0	3	0	0	8	4	16
Barrancabermeja	8	5	2	0	0	2	3	20
Bello	16	16	6	16	8	0	14	76
Buenaventura	1	1	1	1	2	2	1	9
Florencia	7	8	7	7	4	1	5	39
Magangué	4	8	1	8	5	8	12	46
Neiva	15	14	6	11	16	4	3	69
Palmira	12	15	0	13	2	4	4	50
Pereira	13	14	11	14	14	8	11	85
Quibdó	1	1	1	0	1	0	0	4
Riohacha	13	15	16	14	15	0	0	73
San José del Guaviare	5	11	0	7	0	7	7	37
Santa Marta	14	14	12	16	12	6	3	77
Sincelejo	7	11	4	12	2	12	13	61
Soledad	9	6	14	9	11	2	2	53
Tuluá	0	0	2	5	0	2	2	11
Tumaco	16	12	3	16	4	1	2	54
Valledupar	2	0	3	4	2	1	8	20
Villavicencio	12	5	11	1	15	0	9	53
Yopal	13	11	5	11	7	9	9	65
TOTAL	169	167	108	165	120	77	112	918
Average/CITY	9.9	9.8	6.3	9.7	7.1	4.5	6.6	

Values presented include significant correlations found on 2-week and 1-week temporary bases.
TEMP-AVER, average temperature; TEMP-AVERDIF, averaged daily temperatures difference; TEMP-AVERMAX, average of maximum temperatures; TEMP-AVERMIN, average of minimum temperatures; TEMP-MAXABS, maximum absolute temperature; TEMP-MAXDIF, maximum difference of daily temperatures; TEMP-MINABS, minimum absolute temperature.

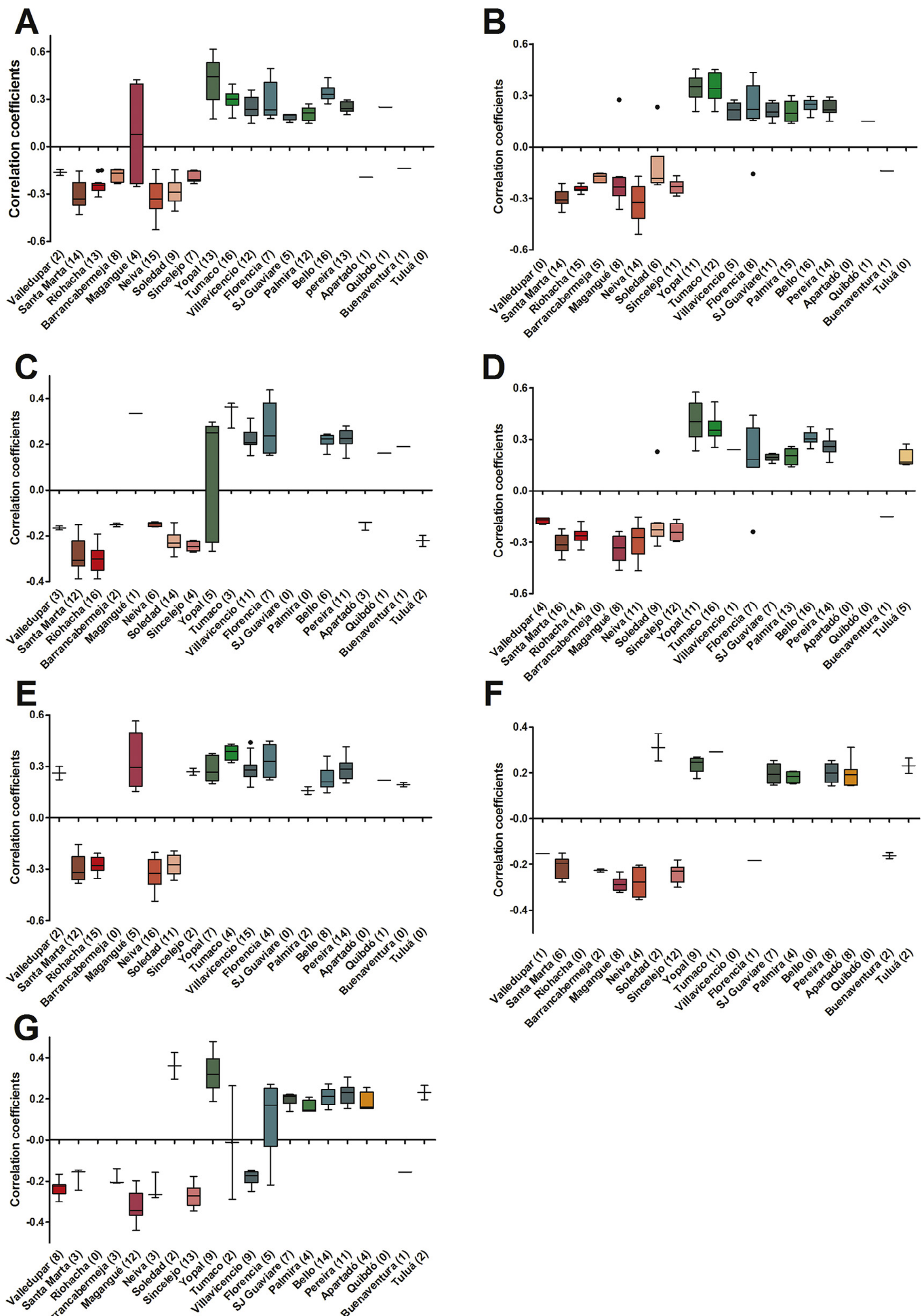

Figure 1. **Values of correlation coefficients (ρ) between different climatic variables and dengue cases for 20 cities from Colombia. Plots show the range of correlation coefficients of variables in each city. The number of significant correlations is indicated in parenthesis next to the name of the city on axis X. Bars in shades of red indicate cities belonging to groups with negative correlations, bars in shades of green are related to those with positive correlations, and bars in shades of orange are related to cities where few or none significant correlations were recorded. (A) Average medium temperature, (B) absolute maximum temperature, (C) absolute minimum temperature, (D) average of maximum temperatures, (E) average of minimum temperatures, (F) maximum difference of temperatures, and (G) average difference of temperature.**

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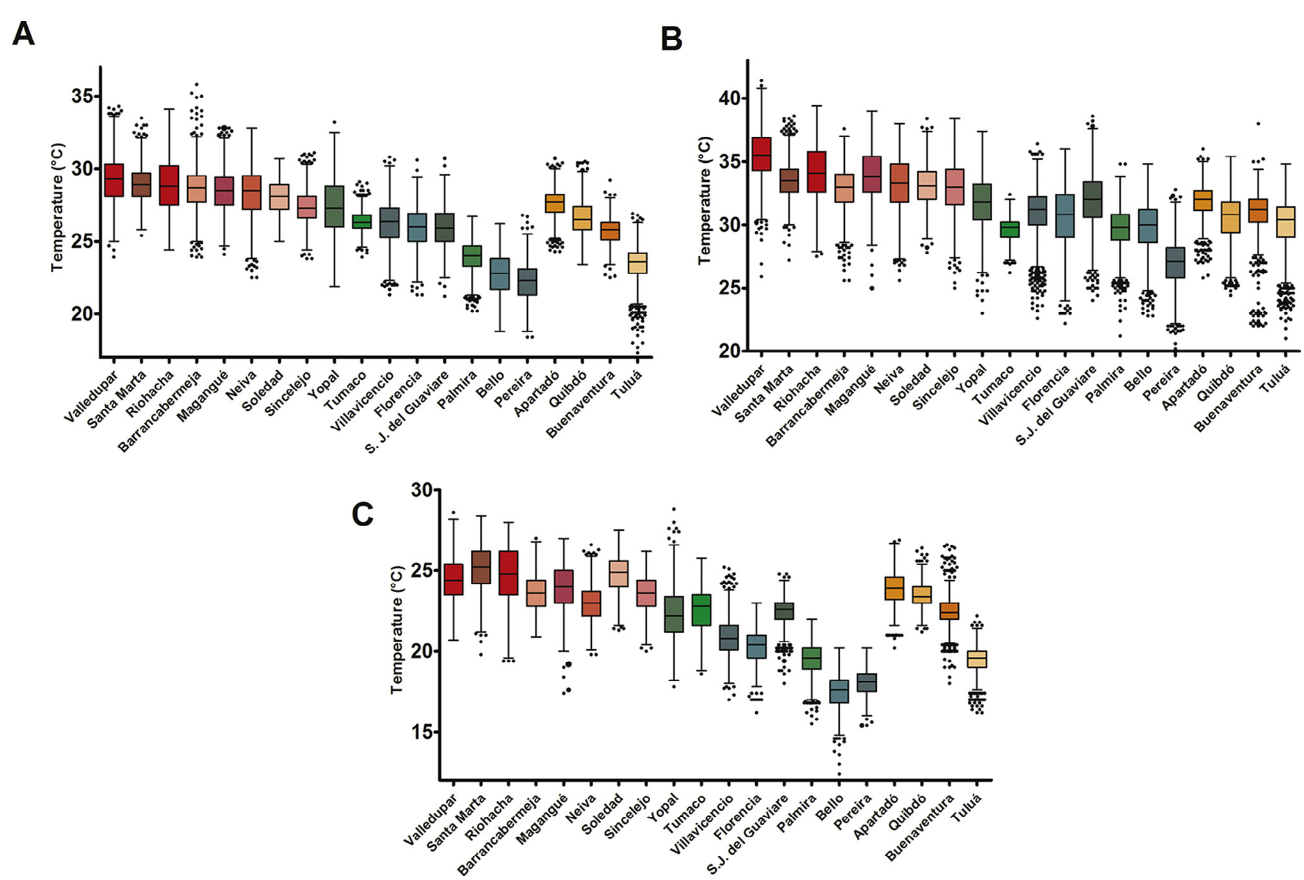

Figure 2. Distribution of values of (A) average temperature, (B) average of maximum temperatures, and (C) average of minimum temperatures for 20 Colombian cities for which Spearman analyses were done. Bars in shades of red indicate cities with negative correlations, bars in shades of green are related to those with positive correlations, and bars in shades of orange are related to cities where few or no significant correlations were recorded.

temperature. However, this does not hold at higher temperatures. On other side, when TEMP-AVER and TEMP-AVERMIN is plotted, the curve is smoother than produced by TEMP-AVERMAX (Fig. 4).

DISCUSSION

Climate is an important factor in determining mosquito behavior and the effectiveness of DENV transmission.[22] The importance of climate and related variables has led to development of numerous models to forecast dengue behavior in multiples cities (reviewed by Louis et al[23] and Naish et al[18]). Although data-driven predictive models are an important goal, first we must understand what variables contribute to differences in dengue incidence and transmission in cities. Temperature is especially important given its known role in transmission on the vector side, expansion of vector ranges, vector life traits, and so on.[7,11,24,25] The availability of climate data also makes using them attractive as a cost-effective, accessible means of prediction. Thus, we investigated how climatic variables related to temperature might explain patterns of reported dengue cases by examining the correlation coefficients resulting from analyses between climatic variables and dengue cases. We also investigated the role of 2 different lag times to optimize our model because most studies look for ways to predict dengue outbreaks related to a specific lag time and do not compare multiple lag times. However, we think that limiting the focus to unique lag time doesn't allow for the inclusion of all sources of variability associate with climate.

Our primary goal was to understand the way climatic variables are associated with dengue incidence in the human population in different eco-epidemiologic scenarios identified across dengue-endemic regions in Colombia. Keeping in mind that such associations can be dynamic, we decided to perform analyses on the cumulative number of

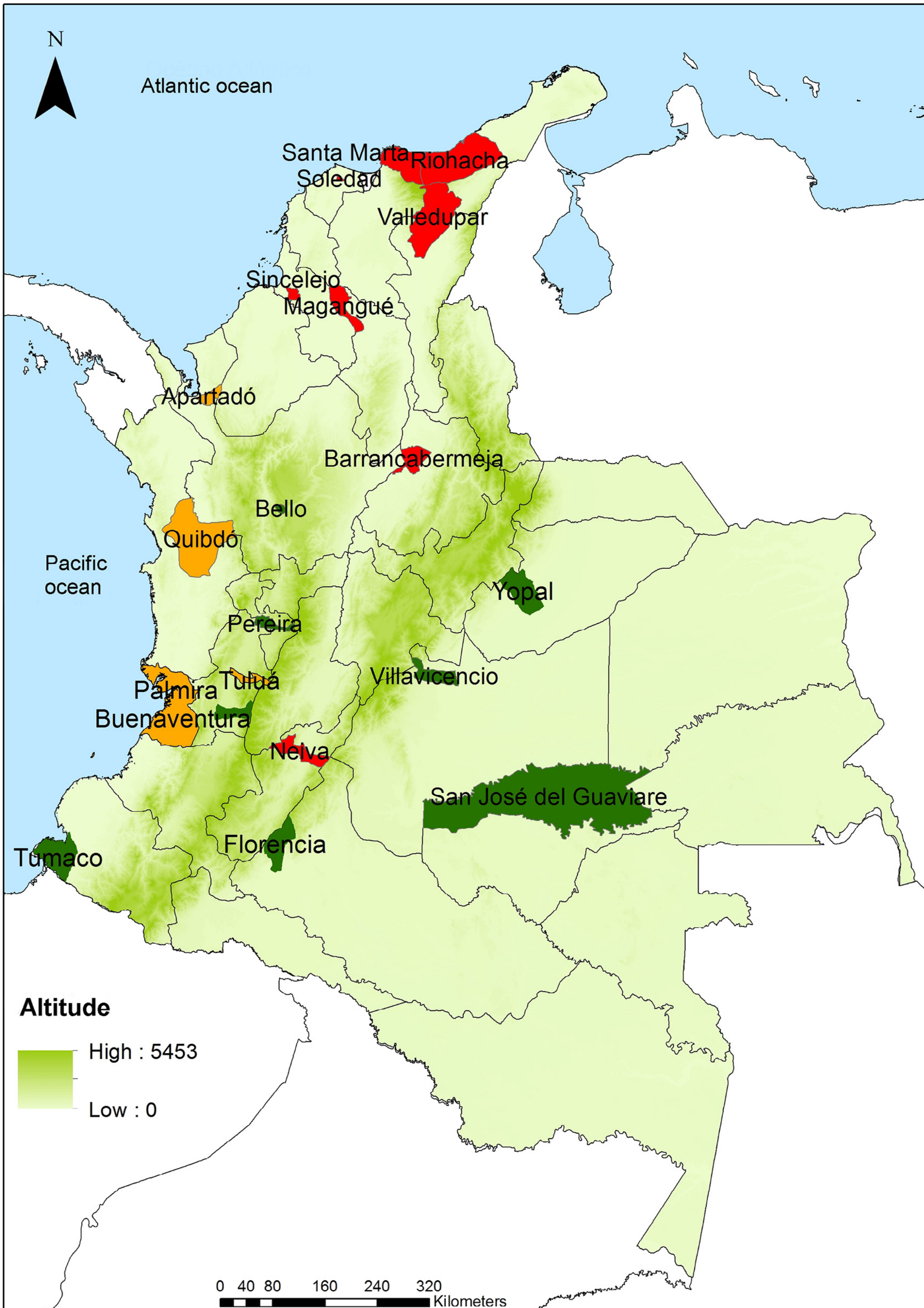

Figure 3. Geographic localization of 20 Colombian cities used in this study. Cities in red are related to those with negative correlations, cities in green are related to those with positive correlations, and cities in orange are related to those where few or no correlations were recorded.

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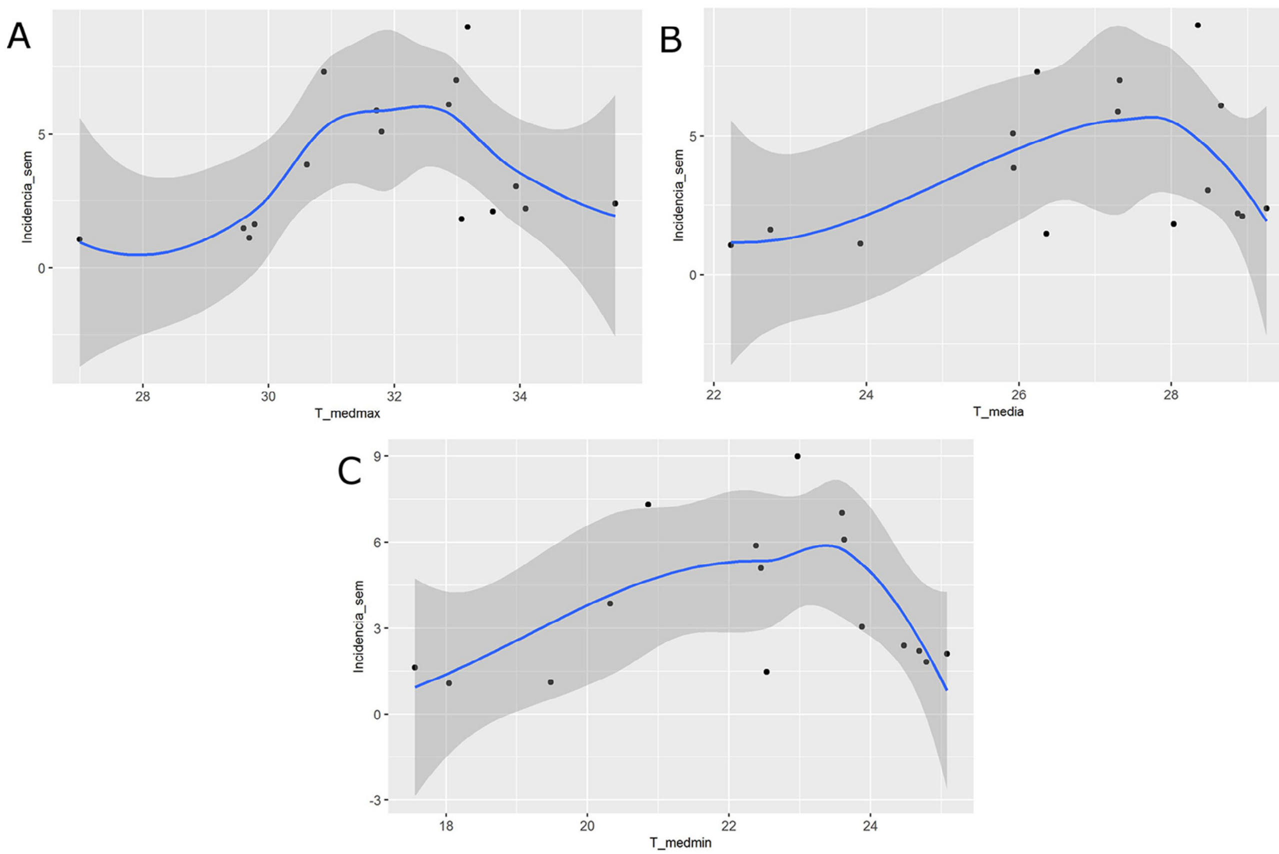

Figure 4. General behavior of incidence across a range of (A) average of maximum temperatures, (B) average temperatures, and (C) average of minimum temperatures according to LOESS analysis. Blue lines indicate the modeled effect, and gray areas correspond to 95% confidence interval of the model. Abbreviations: **Incidencia_sem, weekly incidence estimated according to population projections made by the Departmento Administrativo Nacional de Estadística (DANE) and dengue cases reported by the Instituto Nacional de Salud (INS); T_medmax, average of maximum temperatures; T_media, average temperature; Tmedmin, average of minimum temperatures.**

significant correlations, which gives a better understanding of those variables that are more important related to the reports of dengue cases in these cities.

Taking together the results, 3 groups of populations were defined according to the effect of temperature on the incidence of dengue. The first group displayed significant correlations with negative coefficients. The second group exhibited positive correlations between temperature and dengue cases. These results agree with previous observations developed with vector infection in Colombian cities.[21] A third group was related to cities with no effect of any variables related to temperature characterized by few or none significant correlations. The reason why these cities have few or no significant correlations is unknown. However, we think that the more plausible explanation is that a small number of dengue cases were reported in these cities either because of a lack of symptomatic, reported dengue as a result of a higher percentage of population with African ancestry,[26] which has been associated with less susceptibility to severe forms of dengue disease severe forms[27-29]; or because of an overall underreporting of dengue cases, something that has been noted in ecologically similar cities such as Quibdó.[30]

Taking the number of significant correlations per variable, TEMP-AVER seems to be the most important variable, which suggests that the mean temperature mostly modulates the effect of temperature on dengue incidence, which agreed with previous findings.[20] After average temperature, the most important variables were those related to maximum temperature (TEMP-MAXABS and TEMP-AVERMAX), followed by TEMP-AVERMIN, TEMP-AVERDIF, TEMP-MINABS, and lastly TEMP-MAXDIF. According to these results, higher temperatures are more influential than lower temperatures, and the differences in daily temperatures seem to be less important.

Although most studies report positive correlations between temperature and dengue incidence, some studies have reported some negative correlations. The first report of negative correlation of dengue cases and temperature was done by Yu et al[31] in 2011 in Taiwan, where they explained that such negative correlations were mainly because of effects seen at temperatures higher than 30°C. A more specific result is that recently described by Limper in Curaçao, where a 1°C decrease of mean temperature was associated with a relative risk of dengue incidence of 17.4%, whereas a 1°C increase of mean temperature was associated with a relative risk of 0.457%.[32] However, the findings of this work suggest that those relationships can be positive or negative depending on the mean temperature because each city has a unique relationship between temperature and dengue incidence.

On the other hand, when analyzing the daily ranges of temperature (TEMP-MAXDIF and TEMP-AVERDIF), it was interesting that it was positively associated with dengue cases in the second group but negatively associated in the first group. This result is in line with what Carrington et al[17] reported previously when they suggested that an increase in DENV transmission was affected by the daily temperature range when mean temperature was low. This important result suggests the possibility that cities suitable for the presence of DENV transmission with lower temperatures may have a greater risk of transmission, but it should be further studied with natural populations.

By examining the geographic distribution of the cities with negative correlations, we noted that they are mainly located in northern Colombia and along the Magdalena river basin (Fig. 3). When we examined the map of distribution of multiannual average temperatures provided by IDEAM (available at http://atlas.ideam.gov.co/basefiles/Temp_Med_Anual.pdf), it was noted that high temperatures were mainly concentrated in the north and extending between the central and eastern mountain ranges through the Magdalena river basin, which is concordant with the distribution of cities with negative correlations.

Additionally, the LOESS analyses displayed a model of temperature versus incidence among 16 cities and indicated that an increase in incidence could occur with a gradual increase of average temperature until the temperature was near 28°C, with an upper threshold effect at >28°C, at which point the curve indicates falling incidence (Fig. 4). The points located at the right of the inflection of the curve correspond to cities with negative correlations and higher temperatures. Similarly, Lambrechts et al[13] proposed a model for vector competence as a function of temperature that indicated that the vector competence of the mosquito declines after an average temperature of 28°C, which would indicate a decrease in transmission and is in agreement with our results. Finally, the differences noted between curves produced by TEMP-AVER and TEMP-AVERMIN and that produced by TEMP-AVERMAX (Fig. 4) could indicate that high temperatures might impose a stronger influence than minimum temperatures, which is in agreement with the number of significant correlations.

CONCLUSIONS

Our results suggest that temperature can be associated with incidence in an ecologically stratified manner. The way temperature is related to dengue cases differs across the range of temperatures where higher temperature can affect negatively the incidence. According to previous observations, such negative association is related to mosquito infection, and it affects the incidence in human populations. Low temperatures are positively related to dengue cases, but the highest temperatures seem to have the major effect. Such associations lend further evidence to support that it is the average temperature that mostly governs even the way that daily variations of temperature are related to incidence, and large daily temperature ranges do not necessarily negatively affect transmission. These ideas can have a great impact on how DENV transmission is conceptualized and how predictive models can begin to be built. Taken with our previous results related to temperature and the detection of infectious mosquitoes,[21] ecologically appropriate, targeted strategies for vector control, prioritization of areas with higher probabilities of transmission, and more efficient resource allocation can be developed.

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