Author's response to reviews

Title: Time series analysis of dengue incidence in Guadeloupe, French West Indies: Forecasting models using climate variables as predictors

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Author's response to reviews: see over
Dear Editor,

Please find attached the revised manuscript with tracked changes, entitled “Time series analysis of dengue incidence in Guadeloupe, French West Indies: Forecasting models using climate variables as predictors”. You will also find below a point-by-point response to the concerns of the two reviewers.

Sincerely,

Myriam Gharbi
Reviewer #1

I General Comments

II. Specific Comments

A. ABSTRACT

1. 1st Paragraph: Wrong term needs to be corrected: The 1st sentence in 1st paragraph “During the last decades, dengue viruses have spread throughout the Americas region, with an increase in the number of severe forms of dengue fever.” should be revised as “in the number of severe form of dengue”. The severe form should be “dengue hemorrhagic fever” rather than “dengue fever”.

Answer: OK, we changed the sentence.

Modification: Cf abstract in the revised manuscript p3. “During the last decades, dengue viruses have spread throughout the Americas region, with an increase in the number of severe forms of dengue”

2. In the Paragraph of RESULTS: p-value that p should NOT be capitalized

Answer: OK, we changed all the “P value” by “p-value”.

Modification: Cf revised manuscript

3. Writing Style: The Abstract for a web journal needs to stand out your key points more clearly and make readers feel more interesting to learn. The last sentence of conclusion can mention “public health implication”. It would be much better that the writing in RESULTS can be more concise.

Answer: OK, we modified the abstract to point out our key points in the goal of the study, to concise results and to conclude by the public health implications.

Modification: Cf abstract in the revised manuscript p3. We add these two following sentences.

- Background: “The surveillance system in Guadeloupe (French West Indies) is currently operational, [...] to predict the occurrence of dengue epidemics few months ahead and thus to help an efficient dengue control.”
- Conclusion: “This approach which is practicable for a surveillance system [...] efficient implementation of prevention activities.”

B. BACKGROUND

1. Major Points

a) The author has an idealistic goal of this study by developing a predicable model that can be integrated with surveillance system and thus helps efficient dengue control. This goal is very admirable and practicable. This key point needs to be pointed out very clearly in ABSTRACT.
Answer: Ok, we modified the abstract in order to point out the key points (Cf above) and the aim of the study in the background.

Modification: Cf revised manuscript: abstract and part 1 p7
“The surveillance system in Guadeloupe is currently operational for the detection of early outbreaks of dengue. [...] This predicable model would be used to help an efficient dengue control”.

b) It is not clear about the epidemiology of dengue in your study areas “Guadeloupe”: Please add one paragraph to give readers an idea such as how many total dengue cases, numbers of DHF cases, incidence of dengue over years and whether dengue is endemic in Guadeloupe or not and which serotypes of dengue virus occurred in different years. If the epidemiology of dengue in your study area is not clear, it will be very difficult for readers to follow and judge your method is best one.

Answer: Ok, we added a paragraph to give readers more information about the epidemiology of dengue in our study area.

Modification: Cf revised manuscript Part 1 p5
“In some areas, as the French Overseas Territories of the Americas [...] respectively 11,500 in 2005 (0.4% of severe cases; serotype 4 was predominant) and 19,000 in 2007 (0.8% of severe cases; serotype 2 predominant).”

2. Minor Revision

a) “Dengue is a human arbovirosis transmitted by the female mosquito of the genus Aedes, mainly Aedes aegypti and Ae. albopictus [1].” Should be revised as “Dengue is a human arbovirus disease transmitted by.....”

Answer: OK, we changed the sentence in the revised manuscript.

Modification: Cf revised manuscript Part 1 p5. “Dengue is a human arbovirus disease transmitted by...”

b) “Dengue fever, considered as one of the most important arthropod-borne viral disease in the world, is prevalent in tropical and subtropical regions” should be revised as “Dengue, the most important arthropod-borne viral disease, is prevalent in tropical and subtropical regions. Two major clinical forms of dengue illness involve the mild form of dengue fever and severe form mostly characterized by plasma leakage with or without hemorrhagic fever.”

Answer: OK, we changed the sentence in the revised manuscript.

Modification: Cf revised manuscript Part 1 p5
“Dengue, the most frequent [...] Two major clinical forms of dengue illness involve the mild form of dengue fever and severe form mostly characterized by plasma leakage with or without haemorrhage [2]”.


C. METHODS

1. Major Points:

a) Data Collection: What is the case definition of dengue? Were dengue cases used from suspected reported cases but how about the % of these cases is laboratory-confirmed that is not clear at all. Please write it more clearly.

Answer: Ok, we wrote it more clearly and we added a paragraph to explain the surveillance system in Guadeloupe and why we did not use laboratory-confirmed cases. The other paragraph we added, clarifies the case definition of dengue.

Modification: Cf revised manuscript Part 2.2 p8.

“The sentinel network was set up from 1983 by local health authorities in association with Institut Pasteur in Guadeloupe. Until 2004, dengue-like syndrome reporting was linked to laboratory confirmation done by Institut Pasteur [Error! Reference source not found.]. [...] Thus, laboratory-confirmed cases, which is a less efficient indicator to monitor the dynamics of an epidemic, and syndromes dengue-like counted for surveillance are not directly linked. In this study, the dengue incidence was calculated from the weekly number of dengue-like syndromes and data from the Institut Pasteur were only used for validation purpose of this incidence.”

“A suspected dengue case is defined as a patient with less than seven days of fever (≥38.5°C) without evidence of other cause of infection and with at least one symptom of pain (headache, retro-orbital pain, myalgia, arthralgia, back pain)”.

b) 1st sentence of the 2nd Paragraph: Each week, the total number of dengue fever collected is extrapolated to the whole island using for adjustment the ratio “medical activity of sentinel practitioners present during the week” / “medical activity of all the GPs in Guadeloupe”. Do you mean that numbers of “DHF” would not be counted or NOT. That is very confusing. Please clarify this issue

Answer: In the study, we did not include inpatients. Nevertheless, severe cases treated in hospitals represent less than 1% of dengue cases. Since the goal of the study was to develop a tool to predict outbreaks intensity of dengue, we did not focus on the severity rate of the outbreaks. We added a sentence to clarify this issue.

Modification: Cf revised manuscript Part 2.2 p8:

“Dengue cases reported by practitioners are mainly non-severe; severe cases treated in hospitals are not included but represent less than 1% of dengue cases”.

c) Climate Variables: What is the rationale to choose those your climate variables in this study. Have you systematically reviewed all possible climate variables that may be related to dengue or mosquito in biology? Do you have vapor pressure data that may be much better than humidity?
Answer: In the study, we only used data which have been collected by the French meteorological Institute in Guadeloupe (Méteo France). The variable “Vapor pressure” was not available. Moreover, vapor pressure which is a measure of relative humidity by satellite remote sensing is less pertinent than humidity in our a small territory surrounded by water as the Guadeloupe Island is. Because of the poor resolution of this tool in this context, data collected from a meteorological station on the ground are more relevant.

Modification: Cf revised manuscript Part 4 p14

“1- Vapor pressure which is a measure of relative humidity by satellite remote sensing [45] is less pertinent than humidity in our geographical situation because of the poor resolution in a small territory surrounded by water as the Guadeloupe Island.”

2. Minor Points:

a) SARIMA model equation: It needs to explain it more clearly so that readers can appreciate and learn it faster, such as $(1-B)^d (1-B)^s$.

Answer: Ok, we completed the explanations of the SARIMA model equation.

Modification: Cf revised manuscript Part 2.3 p9-10

“The seasonality as well as the trend is highlighted by plotting the original time series. The presence of these two components determines the choice of a SARIMA model equation:

$$y_t = \frac{\Theta_q(B)\Theta_p(B^s)\phi_p(B^s)\phi_p(B)}{\phi_p(B^s)\phi_p(B)(1-B)^d(1-B^s)^D} (\text{where } \phi_p(B^s) \text{ is the seasonal autoregressive (AR)}$$

operator, $\phi_p(B)$ the AR operator, $\Theta_q(B)$ the moving average (MA) operator, $\Theta_q(B^s)$ the seasonal MA operator, $(1-B)^d$ and $(1-B^s)^D$ the ordinary and the seasonal difference components, $\sigma_i$ the white noise, and $y_t$ the dependant variable”.

b) Processing and data analysis: How did you do and select your univariate model.

Answer: The univariate model has been built using the four steps of Box Jenkins method. To select the model, with fewer parameters that fits the data best, the Akaike Information Criterion (AIC) is used. We detailed later the process of selection of our model (Cf results: part3 p12).

Modification: Cf revised manuscript part 2.3 p9-10 “The seasonality as well as the trend are highlighted by plotting the original time series [...].To select the model, with fewer parameters that fits the data best, the Akaike Information Criterion (AIC) is used. To validate the final model, its residuals are analyzed by the Ljung-Box test. Residuals must be equivalent to white noise”.

c) Unclear about the data calculation: The average monthly cumulative rainfall for dry and wet seasons: how did these average data be calculated?
Answer: Ok, we withdrew this information which is not relevant. The period corresponding to the dry and to the wet season has been defined by the French Meteorological institute.

Modification: Cf revised manuscript Part 2.1 p8 “The climate is tropical with two distinct seasons: a dry season from January to June, characterized by relatively low rainfall and a wet season from July to December”.

d) Historical Data: How long did the historical data cover?

Answer: The historical data cover the period from 2000 to 2007. We added this information in the data collection part.

Modification: Cf revised manuscript Part 2.2 p8 “This study covers the period from 2000 to 2007 for dengue incidence and meteorological data.”

e) Intervention: Did intervention or any public health efforts may affect your dengue incidence? During the study period, had any intervention or other strong effecting event (new serotype of dengue virus, hurricane, etc.) happened

Answer:

- During the period of the study, stable dengue control programs were implemented each year in Guadeloupe.

- We did not study the effect of serotype on dengue incidence because of the non temporal structure of this variable which is needed for SARIMA modelling. However, dengue is endemic in the Caribbean region. The four serotypes are circulating within a period of 10 years. Most of the population has already been exposed to at least one serotype of dengue virus.

- The effect of hurricane in dengue virus circulation is not clear and difficult to take into account in the analyses. However, one of our teams (the Cire Antilles Guyane) tried to assess by a score the impact of the Hurricane “Dean” on the risk of dengue: http://www.invs.sante.fr/publications/basag/Basag2008_9.pdf. A deeper study should be done to evaluate correctly the effect of these strong events on the dengue incidence.

Modification: We added 3 sentences in the limits part and we re-wrote this paragraph to be more clearly for readers. Cf revised manuscript

1- Part2.2 p8 “During the study period, stable dengue control programs were implemented each year in Guadeloupe.”

2- part 4 p14 “Other non climatic factors might explain outbreaks of dengue such as (i) geographical characteristics of the study area (i.e. housing density, climate and agriculture works) and (ii) virus characteristics (serotype or virulence)[...]. Most of the population has already been exposed to at least one serotype of dengue virus.
3- part 4 p14 “3- The effect of hurricane in dengue virus circulation is not clear and difficult to take into account in the analyses. [...] A deeper study should be done to evaluate correctly the effect of these strong events on the dengue incidence.

D. RESULTS

1. Epidemiology of Dengue

a) It is not clear about the major epidemiological characteristics of dengue in the study area, besides incidence rates over years

Answer: We developed in the background (Cf above) the major epidemiological characteristics of dengue in Guadeloupe.

Modification: Cf revised manuscript Part 1 p5

“In some areas, as the French Overseas Territories of the Americas [...] respectively 11,500 in 2005 (0.4% of severe cases; serotype 4 was predominant) and 19,000 in 2007 (0.8% of severe cases; serotype 2 predominant).”

b) How about the relationship of dengue cases in the study area and the neighboring countries? Any roles of imported dengue cases in initiating outbreaks or certain serotypes of dengue viruses have high attack rates in several years like dengue virus serotype 2 in Thailand or serotype 3 in Indonesia? Those information needs to be added for readers because incidence rates will be affected by herd immunity besides climate factors.

Answer: Ok, we developed in a new paragraph (in the background) the relationship of dengue cases in Guadeloupe and the neighboring countries and the role of imported cases in initiating outbreaks.

First, the four serotypes are circulating in the region within ten years meaning that most of the population (more than 10 years) is immune to at least one serotype and incidence rates will not be much affected.

Then, in the study, the effect of circulating serotype has not been included in the model because of the non temporal structure of this variable.

Modification Part 1 p5: “Dengue is endemic in all surrounding countries with the four serotypes circulating in the region within a period of ten years. [...]. It contributes to carry new virus strains but it also participates to introduce non immune subjects in an endemic area. Dengue outbreaks may occur when a high proportion of naïve subjects are concentrated in the same area.”

2. Climate Variables

a) Temperature: “Temperature significantly affected the model for better dengue incidence forecasting but not humidity (P value = 0.03 for minimum temperature lag-5, P-value = 0.02 for
average temperature lag-11 and P-value = 0.31 for humidity lag-7). These results implying that minimum temperature and mean temperature are important. However those differences in time lags are hard to explain.

Answer: (Same answer as the reviewer#2). You will find below some elements for the lags according to each weather variable:

These climatic factors don’t influence directly the incidence of dengue but only indirectly through their effect on the life-cycle dynamics of both vector and virus. From mosquito hatching to human case appearance, several successive phases occur resulting in global cumulative lags observed in our study. These phases include larval and pupa development (10 to 21 days), gonotrophic cycle (3 to 7 days per cycle), extrinsic incubation in mosquitoes (7 to 15 days), incubation in human (1 to 12 days). Depending on the respective lag between the biological cycle or mosquito life-stage and the clinical symptoms, the lag between weather data and incidence data will differ. The lag is expected to be shorter for minimum temperature that is usually associated with adult mosquito’s mortality, longer for relative humidity, both related to adult survival and hatching. On the other side, the mean temperature is involved in all biological cycles of *Ae. aegypti* that take more time to influence the dengue incidence.

Modification: Cf revised manuscript part4 P15-16 “Furthermore, concerning the delayed effect of climatic variables on dengue incidence, [...] The lag is expected to be shorter for minimum temperature that is usually associated with adult mosquito’s mortality, longer for relative humidity, both related to adult survival and hatching. On the other side, the mean temperature is involved in all biological cycles of *Ae. aegypti* that take more time to influence the dengue incidence.

b) Humidity: It is not clear why humidity was NOT important. How about vapor pressure and rainfall data?

Answer: In the literature, it is known that relative humidity and temperature are two important variables [51-60], more than rainfall. However, in Guadeloupe between 2000 and 2007, the relative humidity is a very stable parameter (mean=79.3%, IC 95% [78.9, 79.7]). This very low range of variation might explain the low statistical power for this variable and the difficulty to point out a significant effect of the relative humidity in the SARIMA model.

Modification: Cf revised manuscript part 4 p15 “In the literature, relative humidity and temperature are two important variables [...] the difficulty to point out a significant effect of the relative humidity in the SARIMA model.”

3. Multivariate Analysis:

a) Weak Association among variables: In page 8, the sentence “The followings explanatory variables were the most positively correlated with dengue incidence: lag-5 minimum temperature (Pearson lag-7 relative humidity (r = 0.107, P value = 0.04), (Figure 5). Because of their strong correlations with each other, these variables were included into the model only one at a time. Meanwhile, rainfall was not correlated with dengue incidence. All these correlations were weak (below 0.2). The statistical significance by p-values may be reflected by more numbers of weeks.
Answer: We used a matrix correlation between climatic variables and we found a strong correlations between each other ($r>0.5$, $p$-value<10$^{-5}$).

Concerning the explanatory variables, all the correlations were weak. That might be explained by correlations which were performed between residuals of dengue incidence and those of meteorological variables, after removing trends and seasonality. Thus, a large part of the effect of meteorological variables was already taken into account in the model and only residual correlation after an adjustment on the trend and the seasonality were measured. A significant correlation was detected which means the test is powerful, probably due to the high numbers of observations in the study.

Modification Part 3 p12: “Climatic variables identified as the most correlated to dengue incidence were included one by one, because of their strong interrelationship, [...] lag-11 average temperature ($r = 0.141$, p-value = 0.007) and lag-7 relative humidity ($r = 0.107$, p-value = 0.04), (Figure 4).

Part 4 p13 “Observed correlations are weak since they are measured on residuals after an adjustment on the trend and the seasonality. However, they are statistically significant, which means the test is powerful, probably due to the high numbers of observations in the study.”

b) RMSE: The authors used RMSE to compare the goodness of models. However, it will be more important to know which model can provide better prediction that can be applied to public health practice.

Answer: The RMSE for multivariate model is better than the one of the univariate model. Moreover, collating data from Meteo France and including them in the SARIMA model seem practicable and easily to implement in routine for dengue surveillance in Guadeloupe.

Modification: Cf revised manuscript: Part 4 p13 “However, multivariate model can provide better prediction could be implemented in routine for dengue surveillance in Guadeloupe”.

c) SARIMA model: If the SARIMA model fits well, will it be useful to evaluate any new intervention strategy introduced to this island?

Answer: Yes, this model might be used to evaluate any new intervention strategy introduced in the island.

Modification: Cf revised manuscript: Part 4 p13 “This model, if tested in practice and validated with other set of data, might be useful for the evaluation of new intervention strategies introduced into this island”.

d) Confusion about whether univariate or multivariate model is the best for the FINAL MODEL: Based on the writings “Minimum temperature at lag-5 weeks was the best variable for predicting dengue outbreaks (RMSE = 0.72) but without reaching statistical significance ($P$-value = 0.36) when we compare multivariate and univariate SARIMA models by Wilcoxon test”, it is hard for readers to make better judgment. There has not had final model that guide readers clear.
Answer: The multivariate model is improved compared to the univariate model but without reaching statistical significance.
First, statistical criteria helping to choose the final model are controversial because of the lack of power of the Wilcoxon test. However, multivariate can provide better prediction and might be implemented in routine for dengue surveillance in Guadeloupe. It is feasible for the department of public health in charge of dengue surveillance to collate data from Meteo france and to include them into the model. At least, the effect of strong climatic event would be taken into account only with the multivariate model.

Modification: Cf revised manuscript: Part 4 p13 “In the study, the predictions for the year 2007 per period of 3 months […] It is feasible for the department of public health in charge of dengue surveillance to collate data from Meteo france and to include them into the model. At least, the effect of strong climatic event would be taken into account only with the multivariate model.”

e) Since the model fit well, the authors should indicate a list of the predicting values (exact values instead of model values) for the variables (minimum temperature, average temperature and relative humidity) which can apply to the incidence rate of dengue cases.

Answer: We did not change anything for this comment as the authors are not sure about the expectations of the reviewer.

f) All p-values should use “p” which is NOT capitalized.

Answer: OK, we changed all the “P value” by “p-value”.

Modification: Cf revised manuscript

4. Legends of Figures

a) Figure 1:

1) The Figure title: “Evolution of dengue fever incidence rate in Guadeloupe from January 2000 to December 2007.” should be revised as “Monthly incidence rates of dengue (per 100,000) in Guadeloupe from January 2000 to December 2007”.

2) Extrapolation from weekly notification of dengue-like syndromes by sentinel GP’s. This title is confusing about the case definition, because the dengue cases were reported cases rather than laboratory-confirmed cases. Which one is more right?

b) Figure 2:

1) The Figure title “Boxplot of dengue incidence: They represent the data dispersion over 7 year period for each week of the year.” should be revised as “Weekly incidence Boxplot of dengue from January 2000 through December 2009.”

2) Next sentence should be revised as “The variance is displayed for different transformations a) no transformation b) log transformation, and (c) square root transformation.”
Answer: Following the first advice from the reviewer 2, we replaced the figure 1 by a new one providing time series plots of weather variables to demonstrate the crude relationship between dengue fever and weather variables. We removed the Figure 2 which was not needed.

Modification legend: Figure 1 p25: “Dashed red line: Weekly incidence rates of dengue (per 100,000) in Guadeloupe from January 2000 to December 2007 compared to crude meteorological variables for the same period: A) minimum temperature (blue diamond), maximum temperature (yellow cross) and average temperature (green square); B) relative humidity (blue area); C) weekly cumulated rainfall (blue solid line)”

Modification in the text part 3 p11 “The plot of the observed dengue incidence (Figure 1) showed three major outbreaks in Guadeloupe (late 2001 - early 2002, mid 2005 - early 2006, mid 2007 - late 2007). […]. Dengue incidence was not clearly correlated to weekly cumulated rainfall (Figure 1C). An annual seasonality is identified for all these meteorological variables."

E. DISCUSSION

1. Structure of Writing: Could the authors mention BIG picture first and then talk about details later.

Answer: Ok, we changed the structure of the discussion moving a paragraph from the end to the beginning of the discussion.

Modification: Cf revised manuscript. Part 4 P 13 “We develop a model to improve the surveillance system and thus to help efficient dengue control […]. This model, if tested in practice and validated with other set of data, might be useful for the evaluation of new intervention strategies introduced into this island”.

2. Rainfall: The discussion of rainfall is hard to be linked to your RESULTS

Answer: Ok, we added the results of the correlation coefficients we found between cumulated rainfall and dengue incidence over a period of 16 weeks.

Modification: Cf revised manuscript Part 3 p13 “Meanwhile, rainfall was not correlated with dengue incidence over a range of 16 weeks-lags (r<0.06, p-value=NS)”.

3. Differences in lags in minimum temperature vs mean temperature is NOT clear. “at lag-5 weeks and average temperature at lag-11 weeks were variables the most positively correlated to dengue incidence in Guadeloupe”.

Answer: Minimum temperature influences particularly the mortality of mosquitoes. On the other side, the mean temperature is involved in all biological cycles of Ae. aegypti that take more time to influence the dengue incidence.

Modification: Cf revised manuscript part 4 p15-16 “The lag is expected to be shorter for minimum temperature that is usually associated with adult mosquito’s mortality, longer for relative humidity, both related to adult survival and hatching. On the other side, the mean temperature is
involved in all biological cycles of \textit{Ae. aegypti} that take more time to influence the dengue incidence."

4. Some variables that have not been used in this study should move to future directions to avoid confusion by readers.

Answer: Ok, we moved the paragraph concerning variables which have not been used in the limits of the study in the discussion. We reformulated this part to avoid confusion by readers.

Modification: Cf revised manuscript Part 4 p14 “Secondly, the crude relationship between dengue incidence and climatic variables (Figure 1) shows that modification of the weather does not necessarily affect dengue epidemics while the use of SARIMA modelling, which is more relevant, points out a significant effect of these variables. Some other climatic events not available for the study have not been analyzed: [...]. However, the serotype should not affect so much the occurrence of epidemics because of the endemicity in the Caribbean region and the circulation of the four serotypes within a period of ten years. Most of the population has already been exposed to at least one serotype of dengue virus.”

Reviewer #2

Minor Essential Revisions

This is a well-written, clear and interesting paper that addresses important issues related to seasonal variability on dengue fever in Guadeloupe, French West Indies. Both methods and conclusions obtained from the results are adequate. I have some comments about the presentation of the results as well as about some possible suggestions to be discussed together with the ones already presented herein.

1. I would advise providing original time series plots of weather variables to demonstrate the crude relationship between dengue fever and weather variables. Figure 2 may not be needed.

Answer: Ok (same answer as the reviewer#1). I provided three plots in the same figure showing original time series plots of weather variables to demonstrate the crude relationship between dengue fever and weather variables. I removed the Figure 2.

Modification legend: Figure 1 p25: “Dashed red line: Weekly incidence rates of dengue (per 100,000) in Guadeloupe from January 2000 to December 2007 compared to crude meteorological variables for the same period: A) minimum temperature (blue diamond), maximum temperature
(yellow cross) and average temperature (green square); B) relative humidity (blue area); C) weekly cumulated rainfall (blue solid line)"

Modification in the text part 3 p11 “The plot of the observed dengue incidence (Figure 1) showed three major outbreaks in Guadeloupe (late 2001 - early 2002, mid 2005 - early 2006, mid 2007 - late 2007). [...] Dengue incidence is not clearly correlated to weekly cumulated rainfall (Figure 1C). An annual seasonality is identified for all these meteorological variables.”

2. The authors used a cross-correlation function to test the relationships between weather variables and dengue incidence. Cross-correlation functions were performed on the residuals of the models obtained by applying a SARIMA model. It is advisable to provide more details how the seasonality of weather variables was adjusted. Any extremely values (ie., outliers in SARIMA model ) of weather variables were found?

Answer: The weather variables have been collected by the French Meteorological Institute (Meteo france). The seasonality of meterological data has been adjusted using a SARIMA modelling (Cf table 2). I did not find any inconsistent values or outliers for weather variables.

3. It is not clear if any transformation and differences of weather series were used in SARIMA.

Answer: Ok, we added a small paragraph in results to clarify this point. Only relative humidity and accumulative rainfall were log transformed. We applied a regular differencing for all variables except for minimum temperature and seasonal differencing for all variables except for relative humidity.

Modification: Cf revised manuscript Part 3 p12 “Cumulative rainfall and relative humidity variables were log transformed. A regular differencing was applied for all variables except for minimum temperature. A seasonal differencing was also applied for all variables except for relative humidity. The residuals were kept for the multivariate analyses.”

4. It is advisable to add more data (ie., both 2006 and 2007) to validate the models. Validation for a one year period may not be sufficient to ensure efficient control and prevention.

Answer: The quality of “ancient” data is not as good as recent data. Therefore, the extraction of 2006 data would affect the efficiency of the model and the accuracy of the predictions. But if the model is adopted in the dengue surveillance system, then new data will be added every year and will permit more thorough validation.

5. More explanations are needed for delayed effects of weather variables. Relative humidity at a of lag 7 weeks, minimum temperature at a lag of 5 weeks and average temperature at a lag of 11 weeks were consistent with the development of dengue fever and were biologically plausible?

Answer: Same answer as reviewer #1
Some elements for the lags according to each weather variable:

These climatic factors don’t influence directly the incidence of dengue but only indirectly through their effect on the life-cycle dynamics of both vector and virus. From mosquito hatching to human case appearance, several successive phases occur resulting in global cumulative lags observed in our study. These phases include larval and pupa development (10 to 21 days), gonotrophic cycle (3 to 7 days pro cycle), extrinsic incubation in mosquitoes (7 to 15 days), incubation in human (1 to 12 days). Depending on the respective lag between the biological cycle or mosquito life-stage and the clinical symptoms, the lag between weather data and incidence data will differ. The lag is expected to be shorter for minimum

Modification: Cf revised manuscript part4 P15-16 “Furthermore, concerning the delayed effect of climatic variables on dengue incidence, [...]. The lag is expected to be shorter for minimum temperature that is usually associated with adult mosquito’s mortality, longer for relative humidity, both related to adult survival and hatching and even longer for average temperature which effect is moderate but influences the duration most of the biological cycles.”