**Response to the Subject Editor and Reviewers**

**Manuscript reference number:** JME-2023-0210

**Manuscript title:** Two Decades of Endemic Dengue in Bangladesh (2000-2022): Trends, Seasonality, and Impact of Temperature and Rainfall Patterns on Transmission Dynamics

We would like to thank the Subject Editor and Reviewers for their constructive comments and guidance to improve the paper. Following up on the Editor’s and reviewers' suggestions and recommendations, we have revised the manuscript, and each modification has been highlighted in red. We have modified the whole paper as per the Subject Editor and reviewers’ suggestions. We have also corrected the grammatical mistakes and proofread the manuscript line-by-line. Besides, we have corrected all typos and minor mistakes in the presentation of the manuscript that the reviewer brought to our attention. Our detailed response is found below. We strongly believe that the Editor’s and reviewers’ comments have helped us to improve the presentation, readability, and technicalities of the manuscript. We thank you again for your valuable comments.

**Response to the Subject Editor:**

My first problem was that the JME is an entomological journal, but your paper focuses on human cases and does not present any entomological data beyond calculations in the duration of the EIP. In my opinion, your case data is not clearly defined and is possible suspect.  You mistakenly have interchanged the terms 'number of cases', 'monthly incidence' and 'number of infections' --- these clearly are not the same metrics!

Response:

We agree with the editor that our paper contains more epidemiological information than entomological data. While the editor is the decider, we believe people interested in entomology also show great enthusiasm for the public health impact of vector-borne diseases (VBDs). Our earlier publication which was a “Letter to Editor.” in JME (<https://academic.oup.com/jme/article/58/1/37/5877896> ) was read and cited by a considerable number of readers and authors. The open-access nature of the journal will allow to access the article to the interested readers of VBDs.

We thank you for raising this issue of interchangeable word use- 'number of cases', 'monthly incidence' and 'number of infections'. We have now revised the manuscript and kept the consistent use of wording (number of cases) on data. We also included the case definition of dengue as “Dengue cases were identified based on clinical symptoms (including fever and rash) and/or laboratory tests for IgM or IgG antibodies to DENV, and nonstructural 1 protein (NS-1) of DENV”[1]” in the article.

In addition, I think the temporal patterns presented may have been confounded by

1) improvements to the health care system which now detects/reports a greater proportion of the clinical cases that it did 20 years ago,

2) the arrival of new serotypes of the virus which cause more severe disease, and

3) increases in the size of the urban population due to growth as well as urbanization.  Some of these factors could have been accommodated into a more complex modeling structure.

Response: This is a very crucial point. Many thanks for this. We also believe that the improvement of the healthcare system which helps detect a higher number of cases, introduction of new serotypes, and an increase in urban population have a significant confounding effect. However, it is difficult to obtain data for these confounding factors and incorporate them into a model. In our future study, we plan to add some of these factors into a more complex model and estimate their impact. However, we have acknowledged these factors in the discussion. “We also acknowledged that the increased dengue cases in the recent decade could be a result of multiple factors that we could not include in the analysis. These factors include the improvement of the healthcare system which now detects a greater proportion of clinical cases than in the past, the arrival of new serotypes ode DENV, and the increased size of the urban population”.

In addition, your meteorological data come from a single weather station in Dhaka, but you provide no context for how well these measurements represent patterns throughout the country.  For example, don't rainfall patterns change with elevation?

Response: Thank you for this comment. We have now included the lines below in the limitations to explain the issue.

“Another limitation pertains to our exclusive utilization of weather data from the Dhaka station. Given Bangladesh's relatively small size and the moderate climate variation across the country, we focused our data collection solely on the Dhaka station. Furthermore, a substantial proportion of historical dengue data originates from the Dhaka region.” Page 17, Line 382 to 385.

Your paper will require considerable revision to improve the English presentation, formatting and clarity of data description.  To assist I have edited the attached file using tracked changes.

In agreement with the Reviewer, I found your Discussion section excessively long and could be reduced by careful organization.

Response: We thank you for editing our manuscript. We have now incorporated all the changes and revised them further. We have also shortened the discussion section by half.

Finally, your references require careful proofreading: I found improper capitalization, lack of italics for species names, incomplete references [no volume or pages], etc.

Response: As mentioned in the answer to the previous query, we have now proofread the whole manuscript carefully, and corrected the mistakes, more specifically, improper capitalization, italics for species names, and incomplete references.

**Reviewer: 1**  
  
Comments to the Author:  
Hasan and colleagues evaluated epidemiological data of dengue cases reported in Bangladesh between 2000 and 2022, and correlated incidence with some weather parameters (temperature and rainfall). The topic is very important and the data presented could be useful in understanding the dynamics of dengue in Bangladesh. The paper is generally well-written, and the topic should be of interest to the JME readership, although there is little direct emphasis on vectors.

Also, the paper is quite long, especially the discussion (which should be reduced by at least half), considering the limited new data presented.

Response: We would like to thank you for your comments and suggestions to reduce the discussion section. We have now reduced the discussion section by a half keeping the major points in our discussion.

Additional explanations of the data collection and analyses are needed to evaluate the robustness of the conclusions.

Response: Thank you for this comment. We have now included additional explanations of the data collection and case definition.

Probably, several additional variables need to be considered in the analyses or at least discussed as limitations to the very limited information used to explain changes in dengue incidence and severity, including:  
  
1. The authors must define the term "dengue cases" in this study. Did the study consider "suspected dengue cases", "epidemiological dengue cases," or "laboratory-confirmed dengue cases"? Please clarify in the methods section and throughout.

Response: Thank you for making this comment. We considered the definition given by Bangladesh's Ministry of Health and Family Welfare used in detecting dengue cases. “Dengue cases were identified based on clinical symptoms (including fever and rash) and/or laboratory tests for IgM or IgG antibodies to DENV, and nonstructural 1 protein (NS-1) of DENV”[1]”

2. Contextualize the notification system of dengue cases for the Directorate General of Health Services in Bangladesh. For example, are the dengue cases reported for both public and private healthcare services?  
  
Response: Thank you for your valuable time to make this comment. We included the lines below to contextualize the notification system of dengue cases for the Directorate General of Health Services in Bangladesh.

“The current dengue surveillance in Bangladesh is primarily coordinated by the Management Information System (MIS) of the Ministry of Health and Family Welfare of Bangladesh. The surveillance includes the hospitalized patients diagnosed as infected with the dengue virus in the country primarily from government hospitals except in the capital city Dhaka, where more than 57 private hospitals are included in addition to 20 public hospitals. Outside Dhaka, the central district hospital of each 64 districts and medical college hospitals in each district are also included in the surveillance system.”

3. Were all 244,246 dengue cases reported in Dhaka?  
- If not: The correlation between dengue cases and weather variables should be revised and paired with weather variables and the location of dengue cases. Otherwise, assuming climate variation across Bangladesh, the findings presented could not represent this variation.

Response: We included the below lines in our limitations to explain this issue. We thank you for this important point.

“Another limitation pertains to our exclusive utilization of weather data from the Dhaka station. Given Bangladesh's relatively small size and the moderate climate variation across the country, we focused our data collection solely on the Dhaka station. Furthermore, a substantial proportion of historical dengue data originates from the Dhaka region.” Page 17, Line 382 to 385.

- It all was from Dhaka:  The spatial variation of dengue cases could be investigated across eight administrative divisions using maps throughout time. This could help to understand the most affected locations and periods in Bangladesh in the last two decades.

Response: Before 2018, the dengue cases and deaths data were shared as daily cumulative cases of the country not specific to any district. Although we intended to investigate all cases it was not possible due to the lack of data on each division.

4. As mentioned above, please clarify the data location used for weather analyses (i.e., rainfall and temperature)? Is this for the entire country or only for Dhaka? Please explain this point.

Response: The meteorological data were collected from one weather station located in the capital city of Dhaka as most of the cases (~94%) were reported from Dhaka [2] .

“We used three-hourly temperature and daily rainfall data from only Dhaka, as majority of the cases were reported from Dhaka. We collected those data from Bangladesh Meteorological Department (BMD) over the period 2000–2022 (BMD 2023) for the meteorological station located in Mirpur, Dhaka.” Page 6, Lines 138-141.

5. To normalize the population size variation, the analyses need to be performed using incidence (e.g., cases per 100,000 inhabitants) instead of the absolute number of dengue cases. This applies to Figure 1, Figure 4, Table 1, and Table 2.

Response: As our main aim is to provide predictions on the number of dengue cases, we performed the analysis with the total number of dengue cases in Bangladesh.

6. Primary reference sources should replace secondary reports, such as WHO. For example, in the "Introduction section" (Line 82-90) relates to dengue taxonomy, distribution, and burden. Some primary references could be more suitable such as:  
  
Simmonds et al. ICTV Virus Taxonomy Profile: Flaviviridae. J Gen Virol. 2017 Jan;98(1):2-3. doi: 10.1099/jgv.0.000672. PMID: 28218572; PMCID: PMC5370391.  
  
Messina et al. The current and future global distribution and population at risk of dengue. Nat Microbiol. 2019 Sep;4(9):1508-1515. doi: 10.1038/s41564-019-0476-8. Epub 2019 Jun 10. PMID: 31182801; PMCID: PMC6784886.  
  
Bhatt et al. The global distribution and burden of dengue. Nature. 2013 Apr 25;496(7446):504-7. doi: 10.1038/nature12060. Epub 2013 Apr 7. PMID: 23563266; PMCID: PMC3651993.

Response: We have now replaced the references as suggested.

7. How do the authors address the natural temperature variation across time, regarding findings related to "annual temperature increased by 0.49 °C, and annual rainfall decreased by 314 mm".

Response: Thank you for this comment. We measured mean annual weather variables in two decades and compared them with each other.

8. The rationale for dividing the analysis into two decades (2000-2010 vs 2011-2022) needs to be explained. Instead of this arbitrary separation, the authors might compare the trends across years. This could provide a better picture of the epidemiological dynamics of dengue in Bangladesh across time and, if possible, "space", as suggested above. The same comment above, please consider replacing this type of analysis with incidence instead of absolute number of cases.

Response: Thank you for taking the time to provide this insightful explanation. We outlined the reasoning behind segmenting the analysis into two decades. Over the years, there has been a slight variance in dengue cases. To gain a broader perspective, we chose to examine two significant periods. Furthermore, we have illustrated a year-by-year comparison in Figure 1.

“We consider 2010 as a divider of the period 2000-2022 as the year is close to the median year of the duration. Then, we compared the number of dengue cases, deaths, and weather parameters in two decades (2000-2010 and 2011-2022) using paired sample t-test, aimed at examining and comparing trends, developments, and changes over specific periods.” Page 7,

9. The authors need to address several other drivers and factors, such as the herd immunity in the population (are data available?), increases in vector populations, the introduction of new serotypes of DENV, etc. If not addressed, a paragraph explaining this limitation should be included in the Discussion section. The same limitation relates to the case-fatality ratio. For example, since reinfection by a different genotype increases the risk of severe dengue through antibody-dependent enhancement, this could help to explain the increase of CFR and should be better explored in the Discussion section.

Response: We have added a few lines as seen below to add the discussion on herd immunity and on the case-fatality ratio.

We could not use herd immunity data in our model as there data are not available for different serotypes of DENV in Bangladesh. However, earlier studies show that people living in the capital city and larger cities like Chittagong have higher seroprevalence whereas in the rural areas as low as 3% antibodies foe DENV [3]. This also illustrates a high risk of antibody-dependent enhancement (ADE) through secondary and tertiary infection in large cities.

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10. Please contextualize the vector populations in Bangladesh in the Introduction section or Discussion section. Additionally, consider incorporating the P Index in the current analysis. Please see:  
  
Obolski U, Perez PN, Villabona-Arenas CJ, Thézé J, Faria NR, Lourenço J. MVSE: An R-package that estimates a climate-driven mosquito-borne viral suitability index. Methods Ecol Evol. 2019 Aug;10(8):1357-1370. doi: 10.1111/2041-210X.13205. Epub 2019 Jun 19. PMID: 32391139; PMCID: PMC7202302.

Response: As suggested, we have now added some discussion on vector populations in Bangladesh in the Introduction section. We could not include the pupal index (P index) in the analysis as the data are limited for a few locations and only for a few years, and our data on dengue cases aggregated for the whole Bangladesh not specific to any city. We have included a discussion on the P index [only few reports available] as well as the Bretau index (BI) which was more frequently reported from Bangladesh.

11. Discussion section. First, this section should be more focused on the main findings of this study. Second, please include a paragraph on the limitations of this study before the main conclusion. Third, the Conclusion section should be more concise with a key message about the main findings and their implications for public health. Lastly, please include the potential effect of increased temperature, drought, and altered precipitation on the biology of the vector. Some examples of references are below:  
  
Couper et al. How will mosquitoes adapt to climate warming? Elife. 2021 Aug 17;10:e69630. doi: 10.7554/eLife.69630. PMID: 34402424; PMCID: PMC8370766.  
  
Lowe et al. Combined effects of hydrometeorological hazards and urbanization on dengue risk in Brazil: a spatiotemporal modeling study. Lancet Planet Health. 2021 Apr;5(4):e209-e219. doi: 10.1016/S2542-5196(20)30292-8. PMID: 33838736.

Response: We have now revised the discussion and conclusion section as suggested. We have highlighted the main findings and their implication for the public health context. We also added a discussion on the potential impact of increased temp, drought, and altered precipitation (Page 14). Please read the impact of altered rainfall at the end of the paragraph on rainfall (Page 15).

Minor comments:  
  
Abstract: The second sentence in the conclusion does not reflect the conclusion of the findings of this study.

Response: Thank you for this comment. We have dropped the sentence from the conclusion.

Line 130: The variable section could be renamed a "Procedures section."

Response: We have corrected it now.

Line 132-134. Please define "lag 1" and "lag 2."

Response: We have now defined those terms.

“A lagged variable refers to a value from a prior time point. When studying the meteorological impact on Dengue cases, it's crucial to focus on lag variables. Two critical stages for lag effects should be considered: mosquito development and parasite incubation within the mosquito. The lag times for these stages can vary based on climate, creating a diverse lag distribution at the population level. In the context of monthly data, lag 1 refers to the data from the preceding month, and lag 2 pertains to the data from two months prior.” Page 6 to 7.

Line 126-128. The meteorological data are from one location or multiple locations?

Response: The meteorological data were collected from one weather station located in the capital city of Dhaka as most of the cases (~94%) were reported from Dhaka [2] .

“We used three-hourly temperature and daily rainfall data from only Dhaka, as the majority of the cases were reported from Dhaka. We collected those data from the Bangladesh Meteorological Department (BMD) over the period 2000–2022 (BMD 2023) for the meteorological station located in Mirpur, Dhaka. However, we acknowledged that the weather data of one station might not be representative of the whole country. Historically, more than 90% of dengue cases in Bangladesh were recorded from Dhaka [17] and thus our analysis will be more relevant to the weather changes of Dhaka city rather than the whole country. “

Line 70: The increase in annual temperature is mean? Please clarify.

Response: We have now added the word “mean”.

“Concurrently, the annual mean temperature increased by 0.49 °C, and rainfall decreased by 314 mm.” Page 3, Line 76-78.

Line 83: Italicize Flaviviridae  
  
Response: We have now changed it.

Line 84: Consider removing "the female Aedes species, including"  
  
Response: We have now removed it.

Line 87: replace “are recorded” with “are estimated”  
  
Response: Thank you for this comment. We have now changed it.

Line 91: Consider replacing "infections with different serotypes" with "reinfection with different serotypes."

Response: We have replaced it now.

Line 92: Consider replacing "may result in severe dengue with a higher case-fatality ratio" with "may result in severe dengue, including increasing the risk of fatal outcomes."

Response: We have replaced it now.

Line 94-95: This sentence needs to be revised: change “the hotspots” to “hotspots”.

Response: We have revised it now.

Line 95: Consider deleting "official".

Response: Thank you. We have deleted it.

Line 98: number of cases is based on clinical presentation or laboratory-confirmed? This needs to be clarified throughout.

Response: We have now updated the text with the case definition of dengue cases. “Dengue cases were identified based on clinical symptoms (including fever and rash) and/or laboratory tests for IgM or IgG antibodies to DENV, and nonstructural 1 protein (NS-1) of DENV”. Page 6, Lines 135-137.

Line 100: Please clarify the period most important: monsoon or post-monsoon season.

Response: Our data shows that monsoon is still the primary transmission season while cases are increasing in post-monsoon season. We have now revised the text as “Historically Monsson has been the primary dengue transmission season in Bangladesh although the number of dengue cases has increased during the post-monsoon season in the recent years [4].”

Line 105: How much is "increase sharply"? Please clarify it.

Response: Due to the fact that the number of cases increased by 30,000 from 1,000 cases quickly after 2019 we mentioned a sharp increase occurred.

Line 115-116: I suggest replacing "i) compare the annual and monthly cases in the first [2000-2010] and recent decade [2011-2022]" to "compare the annual and monthly dengue cases between 2000 and 2022".

Response: We have now revised the sentence according to your suggestion.

Line 117: Please clarify clinical parameters  
  
Response: We relied on the data that MIS shared publicly. Clinical data were not shared in adherence to the personal data sharing policy. Thus, we were unable to include any clinical parameters in the manuscript.

Line 125: Consider removing "which was discussed in our earlier article."

Response: We have removed it.

Line 188: I suggest replacing the standard deviation with interquartile dengue cases.  
  
Response: We changed tables and results, accordingly.

“Between 2000 and 2022, DGHS reported a total of 244,246 dengue cases, with an annual mean of 10,619 cases (interquartile range [IQR]: 859.5-5805.5), including 849 fatal outcomes with a case-fatality ratio (CFR) of 0.34%. Between 2000 to 2010, the mean annual number of dengue cases was 2,216 (IQR: 480-3182) which increased over eightfold in the following decade (2011-2022) at 18,321 (IQR: 1405-28429)”

Line 189: Please "indicating" to "with"

Response: Thank you. We have changed it now.

Line 189-190: This sentence needs to be revised; it also seems that the "eight folds" (should be stated eight-fold) difference is not supported by the statistical analysis applied (e.g., p-value = 0.219). Additionally, this sentence appears contradictory to the first sentence of the Results section. Please clarify it.

Response: We have now replaced “fold” with “times” and changed the sentence to avoid confusion.

Line 204: This sentence is unclear about "4292 degree-hour/year of heat" Please clarify this point.  
  
Response: The concept of degree-hour or (degree-day) is relatively new. Degree-hour is an estimate of the number of temperatures an insect is exposed to for a certain amount of time. If a mosquito remains 1 hour at 10 °C, that’s 10-degree-hour equivalent heat. Our estimation showed that an additional 0.49 °C in a year can generate an additional 4292 degree-hour heat in a year. This will allow the extensive incubation period of dengue virus in Aedes mosquitoes much faster as higher temperate is positively correlated with virus development rate in mosquitoes (EIP).

Line 211-221: Could you include the interpretation of GF information instead only the number or more or less than 1? This could help the reader interpret the findings. Same thing for M-K trends analysis and Sen's slope test.

Response: We have now included a sentence as seen below in the method section to make it clear.

“Monthly GF greater than 1 indicates that the number of dengue cases would be more than the number of dengue cases of the previous month while GF less than one mean that the number of dengue case of a new month would be less than the previous month. For example, if there are 100 cases in the month of January, the number of dengue cases in the month of February would be 200 when the value of GF is 2.0 or 50 cases when the value of GF is 0.5 for January”. Page 7,

We also added,

“We also conducted a Mann-Kendall (M-K) trend analysis to determine possible upward or downward trends [5]. The null hypothesis posits no monotonic trend, while the alternative hypothesis suggests the presence of a trend, which could be positive, negative, or non-null. We also performed Sen's slope test to assess variations in annual dengue cases and deaths. The slope greater than 0 indicates an upward trend and less than 0 indicates a downward trend of a given period” Page 8, Lines 189-195.

Line 230-233: Figure 4 shows the stabilization of cases with a range that can increase and decrease. The ARIMA model could also be performed in incidence instead of the absolute number of cases.

Response: One of the main aims of this study is to model and predict the number of cases over time rather than the incidence. The idea behind this is to provide numbers to the Ministry of Health and Public Health institutes so that appropriate measures can be taken to handle these cases in hospitals and other care centers.

Line 248: please discuss potential impacts of increasing temperature on vector lifespan.  
  
Response:

“Increasing temperatures can accelerate mosquito reproduction and shorten the duration of the extrinsic incubation period of the virus allowing a faster transmission potential, increase the biting rate but decrease the daily survival probability of mosquitoes and in greater term expand the geographic range of mosquitoes, impacting disease transmission dynamics.”

Line 259: how does rainfall affect water storage in Bangladesh and impacts on Ae. aegypti populations?

Response: In the greater part of the capital city Dhaka, there is a shortage of regular supply of water, and thus people used to store water from the daily supply when available as well as from rainwater. This might facilitate the breeding of Aedes mosquitoes [6].

Figure 3. Please describe the meaning of the dashed line in the legend.

Response: Thank you for your valuable time. We have now explained it in the figure title. We also added the below line in the method section.

“The horizontal line indicates monthly growth factor 1 (the same number of dengue cases in two subsequent months.” Page 8, Lines 173-174.