**Response to the Reviewer**

**Manuscript title: “The 2023 Fatal Dengue Outbreak in Bangladesh Highlights a Paradigm Shift of Geographical Distribution of Cases”**

**Manuscript reference number: HYG-2024-14065**

We would like to thank the associate editor and reviewers for their constructive comments and guidance to improve the paper. Following up on the reviewers’ suggestions and recommendations, we have revised the manuscript, and each modification has been highlighted in red. We have modified the sections as the reviewers suggested. We have also corrected the grammatical mistakes and proofread the manuscript line-by-line. Our detailed response is found below.

We strongly believe that the reviewers’ comments have helped us to improve the presentation, readability and technicalities of the manuscript. We thank you again for your valuable comments.

**Editor Comments to Author:  
  
Reviewer(s)' Comments to Author:**

**Referee: 1**  
  
Hasan et al reported the 2023 fatal outbreak of Dengue in Bangladesh and highlighting a paradigm shift of geographical distribution of cases.  
  
The manuscript is well-described, and materials and methods used are appropriate for this analysis.  
  
This reviewer noticed the description of festivals related cause in page 12, line 268-275.  
The religious festivals: Eid-Al-Fitr and Eid-Al-Adha, have been celebrating every year. Why did that of 2023 cause the large number of Dengue cases and high fatality rate of Dengue related death compared to those of previous years? Was there any associated factor? It should be discussed in the text.

Response: Thank you. We acknowledge that Muslims in Bangladesh have been celebrating Eid for centuries, with millions of people traveling across the country each year during the holiday. However, in 2023, the Eid vacation coincided with a surge in dengue cases in Dhaka City. The dengue outbreak, which began in 2022, continued throughout 2023, unlike previous years when the country typically experienced significantly fewer cases in February and March (please see table 1 of the article by Haider et al. [1]).

“Up until June 28, when Eid-al-Adha was celebrated, 76% of 6,014 reported dengue cases came from Dhaka [2]. Whereas in the first six months of the year from January to June during the period 2000-2022, an average of only 266 cases were reported nationwide [1]. The sharp increase in dengue cases in 2023 coincided with the Eid festival, which facilitated the spread of the virus as millions of people left Dhaka and surrounding cities, such as Gazipur and Narayanganj, to return to their rural homes.”

**Referee: 2**

(There are no comments.)

**Referee: 3**  
  
The paper titled "The 2023 Fatal Dengue Outbreak in Bangladesh Highlights a Paradigm Shift in the Geographical Distribution of Cases" addresses a critical topic in dengue research, particularly concerning the severe epidemic in Bangladesh in 2023. However, several existing publications utilize the same data from the Bangladesh Ministry of Health and Family Welfare (MoHFH). This includes the paper by Rifa Tamanna Subarna and Zwad AI Saiyan, "Understanding the Unprecedented 2023 Dengue Outbreak in Bangladesh: A Data-Driven Analysis," IJID Regions (2024).

doi: <https://doi.org/10.1016/j.ijregi.2024.100406>.  
  
Subarna et al.'s paper uses data from the MoHFH, Bangladesh, covering the extensive period from January 2022 to December 2023, which includes detailed information on dengue patients from the 8 divisions of Bangladesh with comprehensive analysis. Given this context, it is important to clarify the unique contributions of your paper. Specifically, your paper does not extensively address climatic factors, viral factors, or genotypes associated with severe disease and fatal outcomes.

Additionally, it would be beneficial if you could elaborate on the predictive factors for potential locations for future epidemics and the higher fatality rates in females, as well as provide recommendations for government actions. I would also appreciate it if the authors could explain Figure 2, specifically the reason for hospital stays of seven days or more. This information would greatly enhance the value of your research and distinguish it from existing studies.

Response: Thank you. We also would like to thank you for bringing the paper: Tamanna Subarna and Zwad AI Saiyan, "Understanding the Unprecedented 2023 Dengue Outbreak in Bangladesh: A Data-Driven Analysis," IJID Regions (2024) to our attention. We have now added a discussion of the paper on page 3, lines: 81-93. We have discussed this study with our results.

[Reviewer’s comment: Given this context, it is important to clarify the unique contributions of your paper.]

Many previous studies focused only on division-level analysis, whereas we provided an extensive analysis based on district-level data. Our unique contributions (considering existing literature) in our paper includes-

* incidence of dengue by district
* relative increase and changes in dengue cases by division
* correlation coefficient of dengue cases and deaths
* length of hospital stays of all death cases in 2023
* the relationship of dengue cases with meteorological factors including daily average temperature, total daily rainfall, and average daily relative humidity.

[Reviewer’s comment: Specifically, your paper does not extensively address climatic factors, viral factors, or genotypes associated with severe disease and fatal outcomes.]

We have extensively assessed the association of dengue cases with climatic factors (daily average temperature, total daily rainfall, and average daily relative humidity), and showed in “Result and Discussion” section.

In Result section, on page 11, we have included, “We observed significant correlations between monthly dengue cases and various meteorological parameters in the divisions of Bangladesh, including average temperature (r=0.13, p=0.032), total monthly rainfall (r=0.13, p=0.025), and average humidity (r=0.11, p=0.052).’’

“In the GLMM, a statistically significant positive association was identified between the dengue cases and daily average temperature (IRR: 1.13, 95% CI: 1.11-1.14), daily average relative humidity of the division (IRR: 1.09, 95% CI: 1.08 – 1.10), urban and rural population ratio (IRR:1.04, 95% CI: 1.03-1.04). Daily total rainfall of the division (IRR: 0.99, 95% CI: 0.98-0.99), showed a significantly negative association between dengue cases. Population density and distance from Dhaka also exhibited weak negative associations **(Table 1)**.”

“In the Discussion Section, on page 13, we have included, “We found a conflicting negative association between rainfall and dengue cases [3], which might be because of higher rainfall in the Sylhet division where the highest amount of precipitation is usually observed in Bangladesh. However, the relative humidity was positively associated with increased dengue cases in other countries including Thailand, the Philippines, and Sri Lanka [3].”

Due to limited access and/or availability of data, we were unable to evaluate viral factors or genotypes associated with severe disease and fatal outcomes in our analysis. However, we discussed those factors in our limitations.

On page 16, “Our study has several limitations. The data we presented in this study has been recorded through hospital-based passive surveillance in Bangladesh [4]. The surveillance covers a mere fraction (5%) of the country’s total healthcare facilities [2]. We did not have access to the circulating serotype data for the 2023 outbreak. However, several studies including WHO’s report on the Bangladesh dengue situation revealed that DENV- 2 which reappeared in the country in 2023, became the predominant serotype (62%) along with DENV-3 (29%), and co-infection of DENV-2 and DENV-3 (10%) [5,6]. Earlier, all four serotypes of the dengue virus have been recorded in Bangladesh at different times since 2000 [7,8]. DENV-3 caused a larger outbreak in 2019 and remained a dominant serotype until 2022. DENV-4 reappeared in the year 2022 with co-circulation of DENV-1 and DENV-3 [7].Thus, exposure to heterogenous serotypes in 2023 likely increased the risk of severe dengue infection which has a much higher CFR than the primary infection [9]. While we observed significant differences in dengue incidence and CFR between the southern and northern divisions, potential biases linked to the passive surveillance method cannot be ruled out. While improbable, there’s a chance that district health officials in the southern division may have reported more diligently than those in the northern divisions, despite the reporting system being the same throughout the country.”

Additionally, to assess the association of dengue cases about potential locations and sex, we added the urban-rural ratio and male-female ratio in the predictive model. However, in the adjusted model male-female ratio was not included due to the insignificance of the variable. We included those associations in the Results and Discussion Section.

On pages 15, we have added some recommendations, “To limit dengue virus infections in urban areas, particularly in Dhaka, it is crucial to regularly eliminate mosquito breeding sites and enhance surveillance for active cases (Insert Ref 30). Continuous monitoring of dengue cases will facilitate early detection and help to proactively identify hotspots. Public health authorities can then take swift action to control mosquito populations, isolate infected individuals, and launch public awareness campaigns on preventive measures (Ref 30,31). Early detection and prompt response are key to preventing the spread of dengue and mitigating its impact (Ref 30, 31). Both construction management and residents should avoid storing water at construction sites or in homes during vacation periods. Additionally, it would be important to remain vigilant about early rainfall and rising temperatures, which can increase mosquito populations. Developing a municipal water system to reduce the need for water storage is essential for preventing Aedes mosquito proliferation. Residents storing water for extended periods should take special precautions to avoid mosquito breeding (Ref 32).”

**Referee: 4**  
  
I read with interest a manuscript that addresses a topic that requires attention and a phenomenon that is worthwhile studying and following up going forward.

I have few comments/suggestions and queries for edits and corrections:

• Introduction would benefit from few sentences at the start about Bangladesh population and Dengue spread in previous years, before 2023. Perhaps the second paragraph can go first.

Response: Many thanks for this suggestion. We have now added the following paragraph at the start of page 3. “Bangladesh, a densely populated nation with a population exceeding 172 million, has consistently experienced recurring outbreaks of dengue fever, particularly during the monsoon season (Ref 2). This mosquito-borne disease, transmitted primarily by *Aedes* mosquitoes, has emerged as a critical public health concern, with significant surges in infections reported in 2019, 2021, and 2022, and 2023 (Ref 2). Several factors are likely to contribute to the persistence of these outbreaks, including rapid urbanization, inadequate waste management, and climatic conditions such as heavy rainfall and high humidity, which create optimal breeding environments for mosquitoes (Ref 2-5). Despite governmental initiatives aimed at controlling the spread of the disease, the country's high population density and limited healthcare infrastructure have presented substantial challenges to effectively mitigating the outbreaks.”

• Statistical analysis section, lines 146/147: Using random effects to account for time series effects in the data, needs to be better explained. What time series? What was the time units?

Response: Thank you for your comments. We believe that we have now explained it in a better way.

On page 8, we have added and modified a few lines as suggested “The fixed effects (a measure of association), urban-rural ratio, male-female ratio, population density, distance from Dhaka (capital city), daily average temperature, daily total rainfall, and daily average relative humidity were used to estimate their impact on division-wise daily dengue counts (in number) and are expressed as incidence risk ratios (IRRs) with a 95% confidence interval (CI). Regarding the measures of variation (random effects), location with standard deviation (cluster) and intra-cluster correlation coefficient (ICC) were used. In addition, Akaike information criterion (AIC), Bayesian information criterion (BIC), Coefficient of determination (R2), and Root-mean-square error (RMSE) were used to report the variation of dengue cases at the division level and to test the goodness of fit of the model.”

• Statistical analysis section, lines 144/152, this part needs clarity. Please spell out, the outcome and the predictors used. Time series units of time and the justification for using the term time series rather than a generic longitudinal data. No interrupted time series models or any specific time series models were used.

Response: Thank you for this comment. We have now clarified our outcome and predictor variables used in our model as shown below.

On page 8, we added, “In our model, we used the daily division-wise dengue cases as the outcome variable which is a count variable and the urban-rural ratio (as an urbanization proxy), male-female ratio, population density, distance from Dhaka, and several weather factors as the predictors. Variables with a P-value less than 0.05 in the final model were reported as statistically significant determinants of dengue cases.”

We removed the term “time series data” and replaced it with “longitudinal data”.

• Statistical analysis section, lines 150/151: adjusted incidence rate ratios (IRRs), considering dengue deaths: what is meant by considering dengue deaths, was the outcome death? Incidence of death? The sentence needs to be written clearly to explain what the outcome was and what was meant by considering. As it stands it is confusing and seems to suggest some confounders being considered or accounted for.

Response: We mistakenly added the dengue deaths term, we checked carefully now and removed deaths as our outcome variable is dengue case. In addition, we removed the term ‘considered’ and included the outcome and predictor variables.

• Results, line 169-170: Although males constituted a higher percentage of cases (60 vs 40%), females constituted a greater proportion of deaths (57 vs. 43%); the latter two proportions are unclear, 43% of what? It was indicated earlier that the fatality rate was 0.53% in 2023. Do you mean 0.43%?

Response: Thanks for raising this issue, we revised it. To clarify the percentage, we have rewritten the sentence. In addition, 43% is from total deaths, not the case fatality ratio, where case fatality ratio is 0.53%, defined as the percentage of deaths divided by cases.

On page 8, we have slightly changed the previous line as “Although males constituted a higher percentage of cases (60 vs 40%) among total cases, females constituted a greater proportion of deaths(57 vs. 43%) among total deaths in 2023”.

• Results, lines 178-179, stated that, “The average rainfall for the period 2000 to 2022 was 1915.75 mm whereas in 2023 total annual rainfall increased to 2160.70 mm”:  Using the average, assuming this is the arithmetic mean is not a good summary of rainfall over 23 years. A medina with upper and lower quartiles, would provide a better summary of the rainfall average, and range, within the period described.

Response: Thanks for finding out this issue. We have now added the median with upper and lower quartiles.

On page 8, we modify, “The median rainfall for the period 2000 to 2022 was 1843.1 (IQR: 257.10) mm whereas in 2023 total annual rainfall increased to 2160.70 mm.”

“There was a similar range of temperature between 2023 and the period 2000-2022 (28.25 °C (IQR: 6.26) for the period 2000-2022 vs. 27.06 °C in 2023.”

• Line 186, (2.30 vs. 0.50) are these figures per 1000? Please be consistent in the way you report incidence per 1000 population and percentages. This was noted before. In only the sentence that follow-line 187- 2.9 was reported as per 1000. This is confusing.

Response: Thanks for the comments. We have now included results per thousand population.

On page 8, we have modified it as “The divisions southern to Dhaka had a higher dengue incidence compared to the northern division (2.30 vs. 0.50, p<0,0.01) per thousand population whereas the central Dhaka division had an incidence of 2.90 per thousand population.”

• Line 188, and relative humidity (80.79 vs. 79.08%) than the northern. Please complete the sentence, do you mean relatively higher?

Response: We have now corrected and completed the sentence and added “slightly higher”.

On page 8, “In 2023, the southern divisions recorded slightly higher annual temperatures (27.46 vs. 26.54 °C) and also slightly higher relative humidity (80.79 vs. 79.08%) than the northern divisions”.

• Line 207 stated “There was a parallel trajectory in both Dhaka city and outside until mid-April”. Please edit the sentence for clarity, trajectory of what? And what do you mean by trajectory. Please explain.

Response: We have now revised it (on page 10, line 337) by “Increases in the numbers of dengue cases in both Dhaka city and outside were similar until mid-April.”

• Lines 222/223 stated that “A similar association is evident between population density and dengue cases (r=0.47, p=<0.001) and deaths (r=0.43, p=<0.001) was the latter correlation of 0.43 between death and population density?

Response: Many thanks for this comment. We have now rewritten this sentence in page 10, “For monthly dengue cases and deaths, positive correlations were observed between the population size of the district and the number of dengue cases (*r*=0.44, p=<0.001) and population size of the district and the number of dengue deaths (r=0.43, p=<0.001).”

• Figure 1. Please explain in title whether the number of dengue cases, and the number of deaths per month for the period 2000-2022 are totals or means?

Response: Thanks for raising this. We have now corrected it and added ‘total’.

• Figure 3. A. Please add units to time (X axis) it is not clear 0 to 300 what? Days?

Response: Many thanks for spotting this. We have now corrected the X-axis of the graph by adding “Days (in 2023)” to be consistent with the second graph which gives “Months (in 2023)” in the X-axis.

• Figure 3. second part is complex and should be simplified. A label should be added, is the second part B? for example. Relative changes may be presented in a table below the figure rather than adding an additional reference line to the figure.

Response: Thank you for your comment. Initially, we prepared a draft of the manuscript where the relative changes were shown in a table. However, during revisions with colleagues, we realized that the values were difficult to compare in this format. We found that the results are much easier to compare using this graph, so we decided to retain it.

• Too many figures, some are not needed.

Response: We have included four figures, each containing a few subplots. However, we believe that each figure conveys essential information and enhances the overall clarity and flow of the content. Nonetheless, we welcome your suggestions if you find any figure to be redundant.

• Table 1, results, please add unadjusted IRRs.

Response: “We have now added unadjusted IRRs in Table 1”.

Thank you.