**Global Dengue Epidemic Worsens with Record 14 Million Cases and 9,000 Deaths Reported in 2024 International Journal of Infectious Diseases (THEIJID-D-25-00694)**

Reviewer #1:

The authors used data reported to the World Health Organization to understand the distribution of dengue burden and determinants of dengue related mortality and severity. The idea is interesting.

Dengue severity and fatality used to be more common amongst children but this analysis here suggests that aged populations are more vulnerable now.

Response: In lines 179-182. We added the justification in our limitations “It is possible that both children and older adults are more vulnerable to dengue severity and fatality compared to middle-aged individuals. However, due to the lack of detailed age-category variables in the available data, we were unable to analyze and present dengue severity and fatality across specific age groups.”|

However, it is well known that the rigour of surveillance varies across country or even regions within a country and the data could be skewed by countries with a more rigorous surveillance system. While the global data give us a glimpse of the burden of dengue, the outcome of such analysis is skewed and interpretation may be inaccurate.

Response: In lines 182-186, in response to reviewer comments, we added “Moreover, our analysis is dependent on dengue data reported to and compiled by the World Health Organization (WHO), which may not fully capture underreported or misclassified cases from certain regions. Despite these limitations, the consistency of patterns observed across multiple countries and datasets lends credibility to our findings and helps to highlight important global trends in dengue severity and fatality.”

The analysis in the manuscript does not provide new insights or information. The associations of the determinants with fatality or severity were generally weak, and were used to confirm more robust analysis reported in numerous publications. e.g temp, rainfall, older age groups in some communities etc

Response: Thank you for your feedback. As this is a short article, we were limited in presenting more detailed analyses. Our goal was to share a brief overview of key findings in line with the article requirements, complementing existing literature.

Specific comments

The IRR results need clarity. The comparators amongst most of the IRRs examined were not clear. E.g temperature, rainfall, obesity, aged population - what are the numerator and denominators of the ratios? What do the %s in Table 2 represent?

Response: In lines 108–114, we clarify the IRR results, including the comparators, as well as the numerators and denominators used in the ratios. Further clarification is also provided in the results section below.

“Countries located in the Southern Hemisphere (Incidence Rate Ratio [IRR]: 2.64, 95% Confidence Interval [CI]: 2.54–2.74), those with a high mean annual temperature (IRR: 1.20, 95% CI: 1.19–1.20), and high rainfall (IRR: 1.01, 95% CI: 1.01–1.02) showed a significant association with higher dengue cases per million compared to countries in the Northern Hemisphere, with lower mean annual temperatures, and lower rainfall, respectively. For dengue-related deaths per million population, countries in the Southern Hemisphere (IRR: 4.91, 95% CI: 3.48–6.91) were significantly associated with higher mortality rates compared to countries in the Northern Hemisphere.”

Line 58: Though secondary dengue has a higher risk of becoming severe, both primary and secondary dengue could develop into severe forms.

Response: Bhai

Line 95-106: The description of the global situation could be more organised to have a coherent flow.

Response: Thank you for your valuable suggestion. We have revised the description of the global dengue situation to improve the organization and ensure a more coherent flow of information.

Line 108 and elsewhere, authors stated that "countries located in the Southern Hemisphere..... demonstrated a significant association for country's dengue cases/M". This could largely be skewed by data from Brazil and some other South American countries, where surveillance systems are more robust. If comparable data across countries are available, the north and south hemisphere analysis could better be performed based on latitudes.

Response: Thank you for your valuable suggestion. We agree that the initial Southern Hemisphere finding may have been influenced by countries like Brazil with more robust surveillance systems. In response to your comment, we performed an additional analysis comparing tropical and subtropical regions to provide a more accurate and meaningful geographic differentiation of dengue burden. We have revised the Results and Discussion sections accordingly to reflect these improvements. We appreciate your insightful feedback, which has helped us to strengthen the rigor and interpretation of our analysis.

In lines 94-96: In tropical areas, the cases ranged from 0.23 to 2.51 per million, while in subtropical areas, the cases were notably lower, ranging from 0.04 to 0.26 per million.

In 128-130: To confirm this, this study also conducted an additional analysis comparing tropical and subtropical regions, which provided a more accurate geographic differentiation of dengue burden.

Line 126: other factors determined by the authors could be confounded by many other factors, rather than direct impact as suggested by the authors. E.g. obesity may be associated with the environment and CFR affected by the rigor of the surveillance system, i.e. how much of the dengue iceberg is surfaced.

Response: Thank you for your comment. To address multicollinearity, we checked the Variance Inflation Factor (VIF) scores in all three models. As a result, obesity was removed from two models due to high multicollinearity. Since this is a short article format, we initially did not include these details in the Methods section. However, we have now clarified this in the table footnotes to ensure transparency.

Line 171: Author called for "early detection system for secondary/severe dengue cases." Severe dengue is not confined to secondary cases and secondary cases not always associated with severity. For early detection for severe cases, authors could cite the warning signs described in the 2009 WHO guidance for dengue.

Response: Bhai

Reviewer #2:

Major comments

The study would benefit by making mention of resource disparities between countries when reporting dengue outcomes.

Response: Thank you. We have included the texts

The study would benefit from a figure highlighting the number of dengue cases by WHO region or continent, rather than by northern and southern hemispheres, although this is just a suggestion.

Response: Thank you for the suggestion. We have presented continent-wise dengue cases and deaths in Table 1 and highlighted in the manuscript, which addresses this point. We believe this provides a clear overview as per your recommendation.

Specific comments

Line 26: Just a technical comment: The abstract, highlights, and introduction state that "Dengue virus (DENV) is the fastest-growing mosquito-borne disease worldwide." In fact, dengue, which is caused by the dengue virus (DENV), is the fasting growing arboviral/mosquito-borne disease worldwide.

Response: Replaced

Line 45: Indigenous cases were recorded in mainland Europe and USA. Making mention also of the risk of autochthonous dengue transmission in these regions and more could be useful.

Response: Bhai

Line 51: While rapid urbanization has contributed to creating mosquito breeding sites, how these sites are evolving can be made clearer (i.e., breeding sites are often formed when water accumulates in plant pots, plastic containers, unused car tires in urban regions).

Response:

In lines 52-54, “These sites often evolve through the accumulation of stagnant water in commonly discarded or neglected items such as plant pots, plastic containers, and unused car tires, creating ideal environments for mosquito larvae development and thereby increasing dengue transmission risk.”

Lines 48-57: This paragraph should include a note on the differential impacts of dengue in developing countries (or penurious and neglected regions and populations usually in urban areas).

Response:

Line 124-126: Dengue deaths in the southern hemisphere is likely because there are more dengue cases in the tropical regions of the globe. Brazil and south American countries contribute most to that statistic.

Response:

Line 128: Compounded by the evidence that older people (above 60) experience comorbidities, older populations are also excluded from recent novel vaccine campaigns in 2024 (mainly in the South American context) due to lack of robust clinical trials conducted with this population group. This is perhaps worth mentioning.

Response:

Line 133-146: That Brazil contributed 10M cases to the 14M total cases globally is a significant finding. Disparities exist in the capacities with which countries are able to report dengue cases. Brazil is a very good example of a dengue surveillance system that works. The reason why Brazil contributes greatly to this number may explain this result. Although the discussion does highlight that reporting gaps do exist globally and in Europe, this section may benefit from mentioning that reporting gaps could potentially exist largely due to lack of surveillance resources and tools in poorer, dengue-stricken regions of the globe. Suggest mentioning this in the short limitations section of the discussion. If the WHO platform already mentions this, then the methods section in the piece can include a statement. This paragraph would benefit from providing a deeper description of factors contributing to reporting gaps.

Response:

Line 142-144: The underlying challenge of inequities and disparities in resources between countries even within the same region must be addressed first. Perhaps worth mentioning.

Response:

Line 152-153: Worth mentioning that strides toward developing a viable vaccine are underway in Brazil (Butantan institute). But despite these strides, vaccine access regionally and then globally will take time.

Response:

Line 155: Suggest removing the term treatment here as there is no treatment for dengue. Suggest replacing with 'vector control and dengue prevention' or 'prognosis'.

Response:

Line 159: Suggest removing the term 'treatable'. Although dengue can be managed, there is no treatment.

Response:

Line 167: Different countries have different vector control and dengue prevention programs, strategies and capacities. Suggest rephrasing this sentence to 'Dengue prevention is heavily reliant on vector control and elimination strategies.'

Response:

Line 173: Check grammar.

Response:

Line 167-177: Specific next steps for research on dengue should highlight why it is important to understand the specific risk factors associated with this observed 2x increase in dengue cases between 2023 and 2024. What are some of the research questions that WHO's research agenda on dengue may want to address?

Response:

Table S1: Tanzania is in the WHO Africa region; Reunion in the Indian ocean may not be part of the European WHO region - need to clarify.

Response:

Final thought: Evidence generated from dengue cases in the southern and northern hemispheres are not fascinating because they aren't comparable-the A. aegypti and A. albopictus vectors are not well established yet in most parts of the northern hemisphere-neither are dengue cases by tropical and subtropical region. The north and south do not merit equal attention when discussing research, policy and programs on dengue. It may help to understand why the authors chose this comparison if there was a list of countries in the northern and southern hemispheres provided. Given the objectives of this study, what is most meaningful to readers might be dengue cases by WHO region or continent, which may merit a figure rather than a table.

Response: