**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:**  
Thank you for your comment. Age indeed plays a complex and multifaceted role in determining the risk and severity of dengue infection, shaped by factors such as host immunity, prior exposure to different dengue virus (DENV) serotypes, and immunological mechanisms like antibody-dependent enhancement (ADE).

In dengue-endemic regions, children are typically exposed earlier in life, making them more susceptible to primary infections. Conversely, older individuals are more likely to have experienced multiple exposures to different DENV serotypes over their lifetime, increasing the risk of severe disease outcomes and higher case fatality rates. In our recent analysis of 1,705 fatal dengue cases in Bangladesh, we found that age was significantly associated with case fatality rate (CFR): each additional 10-year age increment was associated with a 30% increase in CFR (estimate: 0.03, *p* < 0.01) [1]. While the precise mechanisms underlying the severity of secondary infections are still under investigation, one key hypothesis involves ADE, wherein non-neutralizing antibodies from a previous infection enhance viral entry and exacerbate disease severity [2].

In response to your comment, we have addressed this apparent contradiction in both the discussion and the limitations of our manuscript. Specifically, in lines 138–139, we added:  
**“**However, in endemic regions, children are disproportionately affected compared to adults, with a relatively higher incidence of dengue haemorrhagic fever (DHF) observed among them.”

We have also acknowledged this complexity in the limitations section (lines 219–238). Finally, we would like to emphasize that the relationships identified in our study are based on ecological (i.e., population-level) data rather than individual-level data. Therefore, we caution against interpreting these associations as causal. This limitation is clearly stated in lines 232–238 of the manuscript.

“These variations between countries necessitate caution when interpreting and generalising the data. We also identified factors influencing national-level dengue cases, deaths, and CFR. However, these findings should not be interpreted at the individual level, and the associations should not be considered causal both children and older adults may be 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 analyse and present dengue severity and fatality across specific age groups.”

Response: We appreciate the reviewer’s comments. As our analysis relies on WHO data, we have acknowledged the limitations outlined by WHO on their website regarding the completeness and consistency of this data. Please read the limitation that we wrote in response to the above query:

*“We collected data from the WHO’s global dengue surveillance platform, which is relatively new and updated from 1st January to 1st December 2024. As a result, our dataset does not fully cover the year 2024. Additionally, the WHO relies on dengue reports from various countries, each of which may use different definitions for dengue cases and dengue-related deaths. Moreover, WHO surveillance data are collected monthly and reflect variability in reporting practices among countries. For instance, some nations report data weekly or biweekly, and retrospective revisions, including negative values, are common due to ongoing data cleaning. As the WHO notes, data availability varies significantly across regions. In Europe, case counts are limited to locally acquired infections only, given the high proportion of imported cases from endemic areas. This distinction can contribute to an underestimation of the actual dengue burden in the region. In the African region, data are currently limited to outbreak-affected countries, and other nations will be included as data become available. These nuances underscore broader challenges in surveillance, where both underreporting and definitional differences can affect accurate global comparisons”.*

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.  
This manuscript examines the ecological relationships between national-level dengue incidence (cases per million) and fatality (case fatality rate and deaths per million), incorporating a range of explanatory variables. These include population density, proportion of urban population, national prevalence of obesity, and the proportion of the population aged 65 and over. We also included climatic and environmental factors such as average annual temperature, total rainfall, air quality index, and geographical location (northern vs southern hemisphere) **across 105 countries.** We believe this represents a comprehensive analysis for a single year. Please see Table 2 for details.

We agree that incorporating data from multiple years and more detailed information on comorbidities would enhance our understanding of dengue incidence, severity, and mortality. However, it is important to note that global dengue surveillance remains a relatively new initiative under the World Health Organization (WHO). Comprehensive and standardised data on dengue cases are only fully available from 2023 onwards, with historical data limited to a small number of countries. Consequently, we were unable to include additional years in our analysis. Moreover, our primary objective was to explore the potential explanations for the unprecedented number of dengue cases and deaths recorded in 2024. Expanding the analysis to include longitudinal data or more granular clinical variables would exceed the scope and capacity of this manuscript.

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:

We thank the reviewers for their insightful comment regarding the interpretation of the Incidence Rate Ratios (IRRs). We have estimated IRRs using a generalised linear regression model with a Poisson distribution and a log link function. In this model, the IRR represents the multiplicative change in the incidence rate of dengue (cases per million population) associated with a one-unit increase in the explanatory variable, while controlling for other covariates in the model. Please see at page 4-5:

To clarify:

*“The IRR represents the multiplicative change in the incidence rate of dengue (cases per million population) associated with a one-unit increase in the explanatory variable, while controlling for other covariates in the model. For example, for the aged population, the IRR of 1.04 indicates the deaths per million population increased by 4% with a 1% increase in the proportion of the population aged 65 years and over in the country. “*

The data presented in Table 2 are national-level data. Thus, the first variable ‘Aged 65 and above (%)’ indicated the percentage of people with ≥ 65 and above in each country. Similarly, ‘Urban population (%)’ indicates the percentage of people living in urban areas in each country. We have now clarified this in the table titles, i.e., “*data from a total of 105 countries are included in the model”.*

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

Response: Thanks, we have revised the sentence as “*A primary infection with any serotype of DENV can lead to severe dengue, however, individuals infected for the second time with a different dengue serotype can more frequently develop severe secondary dengue infection”.*

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. Please see line 94-119 under the title “**Global dengue cases and deaths in 2024”**

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. In lines 105-107, we added: In tropical areas, the cases ranged from 0.23 to 2.52 per million, while in subtropical areas, the cases were notably lower, ranging from 0.04 to 0.26 per million.

In lines 138-140, we added: 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: As this analysis presents ecological associations between dengue incidence (cases per million) and dengue-related fatalities (deaths per million and case-fatality rate) and a set of explanatory variables, we limited our model to factors that are both commonly reported to be associated with DENV infection and mortality, and for which reliable, comparable national-level data are available. We acknowledge that several additional variables of interest could enrich this analysis, and we intend to explore these in greater detail in a future, full-length article. We have further explored the data, and because of high collinearity, we dropped Obesity from the final model.

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:

Thank you for this important observation. We agree that while secondary infection is a known risk factor for severe dengue, it is not the sole determinant, and not all secondary infections result in severe disease. Severe dengue can also occur during primary infection, particularly in vulnerable populations such as infants, the elderly, or those with comorbidities. [This has been updated in the background section, e.g., line 64].

We appreciate the suggestion to reference the 2009 WHO guidelines, which provide a well-established framework for the early detection of severe dengue through clinical warning **signs**. In response, we have revised the relevant section of the manuscript to reflect a broader and more evidence-based approach to early detection. Specifically, we now acknowledge the importance of recognising the WHO warning signs—such as persistent vomiting, mucosal bleeding, lethargy, clinical fluid accumulation, and rapid decline in platelet count[1]—which are critical for identifying patients at risk of progressing to severe dengue, regardless of their infection history. We have cited the 2009 WHO guidance accordingly. [Line 181-185]

**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 in lines 192-200.

“There are significant disparities in national dengue reporting capacities. Brazil provides a strong example, with dengue designated a notifiable disease since 1961 and electronic reporting via the SINAN system implemented since 1993. Its surveillance infrastructure is robust, featuring mandatory case reporting, broad diagnostic capacity, and active monitoring at both national and local levels. This facilitates more comprehensive case detection than in many countries where underreporting is common due to weaker health systems. Furthermore, as primary dengue infection is often mild, healthcare-seeking behaviour—particularly in low- and middle-income countries—can further limit case detection, as individuals may only present when severely ill[2]”

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, Supplemental Figure S3, 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: Reworded as per the suggestion.

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: reworded. Please see line 45-46.

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: Thanks for this insight. In lines 53-55, we added, “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: Thank you for your comments. In lines 58-60, “The impacts of dengue are disproportionately severe in developing countries and among urban populations in penurious or neglected areas, where limited access to healthcare and vector control exacerbates disease burden.”

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: Thanks for raising this issue. In lines 138-140, “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 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: Added. Please see line 147-148.

*“Furthermore, older populations are also excluded from recent novel vaccine campaigns in South America due to a lack of robust clinical trials conducted with this population group”*

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.

Response: Thank you. We have now included the discussion.

In lines 192-200, There are significant disparities in national dengue reporting capacities. Brazil provides a strong example, with dengue designated a notifiable disease since 1961 and electronic reporting via the Notifiable Diseases Information System (SINAN) implemented since 1993[3]. Its surveillance infrastructure is robust, featuring mandatory case reporting, broad diagnostic capacity, and active monitoring at both national and local levels[3] . This facilitates more comprehensive case detection than in many countries where underreporting is common due to weaker health systems. Furthermore, as primary dengue infection is often mild, healthcare-seeking behavior, particularly in low- and middle-income countries, can further limit case detection, as individuals may only present when severely ill[2].”

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:** We have revised the Limitation section and cited WHO as the also referring to the lack of resources in reporting cases and completeness of the database. Please see lines 219-238.

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: Thanks, revised the Limitation section. Please see lines 222-232, “Reporting gaps could potentially exist largely due to lack of surveillance resources and tools in poorer, dengue-stricken regions of the globe. WHO surveillance data are collected monthly and reflect variability in reporting practices among countries. For instance, some nations report data weekly or biweekly, and retrospective revisions, including negative values, are common due to ongoing data cleaning. As the WHO notes, data availability varies significantly across regions. In Europe, case counts are limited to *locally acquired infections* only, given the high proportion of imported cases from endemic areas[4]. This distinction can contribute to an underestimation of the actual dengue burden in the region. In the African region, data are currently limited to outbreak-affected countries, and other nations will be included as data become available. These nuances underscore broader challenges in surveillance, where both underreporting and definitional differences can affect accurate global comparisons.”

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: Lines 168-171, Notable progress in dengue vaccine development is underway in Brazil, led by the Butantan Institute, though broad regional and global access may still take time.”

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: Done

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

Response: Done

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: Accepted and rephrased (Line 202-203)

Line 173: Check grammar.

Response: Thank you – we checked the grammar throughout the manuscript for consistency and corrected the typos and grammar.

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: We included this in lines 235-2428, “Future dengue research should prioritise understanding the drivers behind the twofold increase in cases between 2023 and 2024. Key areas include the effects of climate anomalies such as El Niño on mosquito distribution, the impact of rapid urbanisation and land use changes, the role of co-circulating serotypes in transmission dynamics, and viral evolution influencing disease severity and spread[5]. Further priorities include identifying barriers to timely diagnosis and reporting in high-burden regions, evaluating scalable innovations in vector control and surveillance, and optimising vaccine deployment strategies across diverse settings [5]. These research directions closely align with the WHO agenda and are vital for guiding targeted interventions and strengthening global dengue preparedness.

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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: Thank you for the observation. We have clarified the regional classification of the countries mentioned. Tanzania is part of the WHO African Region, while Réunion, despite being a French overseas territory, is also included in the WHO African Region—not the European Region—based on WHO regional groupings.

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:

Our intention in comparing dengue data by hemisphere was to explore broad ecological and climatic contrasts. However, we acknowledge that this approach has limitations due to differences in vector establishment and dengue endemicity, particularly in much of the northern hemisphere. We have revised the manuscript to clarify this rationale and now provide a list of countries by hemisphere in the supplementary material **(Table S1, columns added to indicate the hemispheres. We** have also included a figure showing dengue cases by WHO region (**Fig S3**) to offer a more meaningful and policy-relevant comparison.

References:

1. WHO. Dengue: guidelines for diagnosis, treatment, prevention and control [Internet]. Geneva, Switzerland; 2009 [cited 2025 May 6]. Available from: https://www.who.int/publications/i/item/9789241547871

2. Ng TC, Teo CH, Toh JY, Dunn AG, Ng CJ, Ang TF, et al. Factors influencing healthcare seeking in patients with dengue: Systematic review. Tropical Medicine & International Health. 2022 Jan 27;27(1):13–27.

3. Gurgel-Gonçalves R, Oliveira WK de, Croda J. The greatest Dengue epidemic in Brazil: Surveillance, Prevention, and Control. Rev Soc Bras Med Trop. 2024;57.

4. WHO. Global dengue surveillance : https://worldhealthorg.shinyapps.io/dengue\_global/. WHO. 2024.

5. eClinicalMedicine. Dengue as a growing global health concern. EClinicalMedicine. 2024 Nov;77:102975.