Enfermedades Infecciosas y Microbiologia Clinica 44 (2026) 503144

Contents lists available at ScienceDirect

Enfermedades Infecciosas y Microbiologia Clinica

journal homepage: www.elsevier.es/eimc

Letter to the Editor

Interpreting the role of dengue virus serotypes in adult disease severity

Interpretación del papel de los serotipos del virus del dengue en la gravedad de la enfermedad en adultos

Dear Editor,

We read with interest the article by Dinkar and Singh exploring the relationship between dengue virus (DENV) serotypes and clinical severity in hospitalized patients from northern India.[1] The authors provide valuable data on circulating serotypes and clinical outcomes, and their work contributes to the ongoing discussion on serotype-specific risk stratification. However, we would like to raise some questions that may help contextualize the interpretation of DENV-2–associated severity and mortality in adults.

One aspect that deserves further consideration is the lack of differentiation between primary and secondary dengue infections. While the manuscript appropriately highlights the role of immune mechanisms such as antibody-dependent enhancement, the study design did not allow classification of cases according to prior dengue exposure. In an endemic setting such as northern India, cumulative exposure is common, making secondary heterologous infection biologically plausible for a substantial proportion of adult patients. Given that secondary infection is one of the strongest predictors of severe dengue and mortality, independent of serotype, the observed association between DENV-2 and adverse outcomes may in part reflect underlying immune status rather than intrinsic serotype virulence.[2,3]

Evidence from adult cohorts suggests that the relationship between DENV-2 and mortality is less consistent than that observed in pediatric populations. While DENV-2 has been repeatedly linked to severe disease in children, particularly during secondary infections,[4] studies in adults that adjusted for immune status and comorbidities have shown that DENV-2 does not necessarily confer a higher risk of severe dengue or death. In a large prospective adult cohort from Singapore, DENV-1 rather than DENV-2 was associated with severe disease after adjustment for primary versus secondary infection.[5] Similarly, adult data from Taiwan indicate that mortality is more closely related to disease severity, age, and comorbidity than to infecting serotype alone.[6] In a large Brazilian study (2014–2024),[7] DENV-2 was associated with higher case-fatality and mortality but the excess severity linked to DENV-2 was largely attributed to its greater involvement in secondary heterologous infections, rather than to serotype virulence alone. These observations suggest that, in adult populations, serotype-specific effects should be interpreted within a broader clinical and immunological context.

Moreover, different DENV-2 genotypes (such as the Cosmopolitan genotype DENV-2 genotype II and the American/Asian genotype DENV-2 genotype III), may exhibit heterogeneous virulence profiles and have been implicated in severe disease across different settings.[7,8] Together, these findings underscore that the observed association between DENV-2 and increased mortality is likely driven by a complex interplay between serotype, infection sequence, and genotype-specific viral characteristics, highlighting the need for future studies to systematically incorporate markers of prior dengue exposure and viral genotyping when assessing serotype-specific severity.

The reported case fatality rate of 21.6% in the study by Dinkar and Singh is notably high compared with most hospital-based adult dengue series, even those from tertiary referral centers.[6,9,10] While the authors reasonably attribute this to referral bias and inclusion of severe cases, such an outcome distribution may influence multivariable analyses. In this context, the wide confidence intervals observed for DENV-2 in the adjusted models likely reflect the limited number of fatal events and highlight the inherent uncertainty around effect size estimates.

Additionally, comparative analyses involving serotypes represented by very small numbers, such as DENV-1, should be interpreted cautiously, as they are unlikely to provide stable estimates. Likewise, although age is a well-recognized modifier of dengue outcomes, age-stratified analyses within the adult population were not presented and might have further clarified whether the observed mortality signal was influenced by age distribution rather than serotype predominance.

The population included in the study were not vaccinated for dengue. The TAK-003 vaccine uses DENV-2 as backbone, so it would also be of interest to observe if there are any differences in clinical course according to vaccination status in different serotypes once the vaccine is widely introduced.

Overall, the study by Dinkar and Singh offers important regional insight into dengue epidemiology and reinforces the need for continued investigation into serotype-specific patterns of disease. Further work incorporating immune-status classification, viral genotyping, vaccination status and age-stratified analyses will be particularly valuable in endemic settings, where prior exposure is common and the interaction between serotype, host immunity, and clinical outcomes remains a key area of discussion for clinicians and public health practitioners alike.

Author contributions

MDM is the author of the letter to the editor and wrote it. JLLG reviewed and contributed to the article; RDM reviewed and contributed to the article; MA reviewed and contributed to the article. All authors approved the final version.

Ethical considerations

This work does not involve the use of human subjects.

Informed consent

Not required.

https://doi.org/10.1016/j.eimce.2026.503144

2529-993X/© 2026 Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica. Published by Elsevier España, S.L.U. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Use of artificial intelligence

It was used for style and grammar correction.

Funding

The authors declare no external funding.

Conflict of interest

None.

References

1. Dinkar A, Singh J. Dengue serotypes and their severity correlation: a hospital-based observational study. *Enferm Infecc Microbiol Clin*. 2025:503074. Ahead of print.
2. Halstead SB. Neutralization and antibody-dependent enhancement of dengue viruses. *Adv Virus Res*. 2003;60:421–467, http://dx.doi.org/10.1016/s0065-3527(03)60011-4.
3. Guzman MG, Harris E. Dengue. *Lancet*. 2015;385:453–465, http://dx.doi.org/10.1016/S0140-6736(14)60572-9.
4. Vicente CR, Herbinger KH, Fröschl G, et al. Serotype influences on dengue severity: a cross-sectional study on 485 confirmed dengue cases in Vitória, Brazil. *BMC Infect Dis*. 2016;16:320, http://dx.doi.org/10.1186/s12879-016-1668-y.
5. Yung CF, Lee KS, Thein TL, et al. Dengue serotype-specific differences in clinical manifestation and risk of severe disease in adults Singapore. *Am J Trop Med Hyg*. 2015;92:999–1005, http://dx.doi.org/10.4269/ajtmh.14-0628.
6. Liu LT, Huang SY, Lin CH, et al. The epidemiology and identification of risk factors associated with severe dengue during the 2023 dengue outbreak in Kaohsiung City, Taiwan. *Travel Med Infect Dis*. 2025;65:102852, http://dx.doi.org/10.1016/j.tmaid.2025.102852.
7. Bermudi PMM, Palasio RGS, Pirani M, et al. Dengue incidence, mortality, and case-fatality in Brazil: spatial patterns, socioeconomic contrasts, and serotype impact. *Travel Med Infect Dis*. 2025;68:102934, http://dx.doi.org/10.1016/j.tmaid.2025.102934.
8. Suppiah J, Ching SM, Amin-Nordin S, et al. Clinical manifestations of dengue in relation to dengue serotype and genotype in Malaysia: a retrospective observational study. *PLoS Negl Trop Dis*. 2018;12, http://dx.doi.org/10.1371/journal.pntd.0006817, e0006817.
9. Thein TL, Leo YS, Fisher DA, et al. Risk factors for fatality among confirmed adult dengue inpatients. *PLOS ONE*. 2013;8, http://dx.doi.org/10.1371/journal.pone.0081060, e81060.
10. Tsheten T, Clements ACA, Gray DJ, et al. Clinical predictors of severe dengue: a systematic review and meta-analysis. *Infect Dis Poverty*. 2021;10:123, http://dx.doi.org/10.1186/s40249-021-00908-2.

Marta Díaz-Menéndez [a,*], Jara Llenas-García [a,b], Rosa de Miguel Buckley [a], Marta Arsuaga [a]

[a] *National Referral Centre for Tropical Diseases and International Health, Hospital La Paz-Carlos III, IdIPaz, CIBERInfec, Madrid, Spain*
[b] *Universidad Miguel Hernández, Elche, Spain*

[*] Corresponding author.
E-mail address: marta.diaz@salud.madrid.org (M. Díaz-Menéndez).