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Editorial

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Dengue severity in travellers: challenges and insights

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Dengue is the most common arboviral disease globally and is caused by infection with one of four immunologically distinct dengue viruses serotypes (DENV1–4).[1] Most dengue infections are asymptomatic or associated with a benign febrile illness and only a minority of infections progress to severe disease. Immune responses to dengue play a crucial role in determining the likelihood of clinical disease and its severity.[2]

In primary dengue infection, individuals typically gain lifelong protection against the infecting serotype (homotypic protection) and temporary cross-protection against the others (heterotypic protection). [1] Modelling studies based on data from endemic settings suggest that ~18% (95% CI: 16–20%) of primary dengue infections are symptomatic.[3] For secondary infections, the proportion of cases that are symptomatic varies with the time since primary infection. It is lower, at ~13% (95% CI: 5–17%) in those infected within a year of primary infection, and rises to ~41% (95% CI: 36–45) for secondary infections occurring after the first year.[3]

Severe dengue can occur in both primary and secondary dengue infections, but in endemic populations it is most strongly associated with secondary infections, likely due to antibody-dependent enhancement.[1,2] A recent meta-analysis estimated that secondary infections are more than twice as likely to cause severe disease than primary infections [OR 2.26 (95% CI 1.65–3.09)].[2] Severe dengue is estimated to occur in ~2–4% of secondary cases.[1]

Dengue is now the leading cause of febrile illness in returned travellers from all continents except Africa.[4,5] A recent publication estimates an incidence rate of 6 symptomatic dengue infections per 1000 unvaccinated travellers to endemic areas per month.[6] Although dengue causes substantial morbidity in travellers from non-endemic regions, most cases are primary cases and severe dengue is rare.[4,6] The extent to which data on severe infection derived from endemic settings can be extrapolated to travellers remains uncertain.

In this issue of the Journal of Travel Medicine, Avrami and colleagues present findings from a retrospective cohort study comparing clinical and laboratory parameters in cases of primary vs secondary dengue in travellers.[7] The study encompassed patients diagnosed with dengue over a 12-year period in Israel, with 245 out of 425 cases (58%) having complete diagnostic data for analysis. A key criterion used to differentiate primary from secondary dengue was the IgG to IgM ratio during the first week after symptom onset, using a threshold of $\geq$1.3 for secondary infection. Severe dengue was based on WHO criteria.[8]

Of the 245 included cases, 210 (86%) were categorized as primary and 35 (14%) as secondary infections. The authors identified two parameters that differed significantly between groups: longer fever duration in secondary cases (6.4 days vs. 5.3 days, $P = 0.027$), and higher mean aspartate aminotransferase (AST) levels in primary cases (146 vs. 65 U/L, $P < 0.001$). Four patients (all with primary infections) met criteria for severe dengue, with no fatalities. The authors concluded that secondary dengue in travellers does not exhibit a consistent trend of greater severity in clinical and laboratory markers.

This conclusion has been carefully worded, but readers should take care not to be misled considering key limitations. First, there are issues with the authors' interpretation of the clinical and laboratory markers and conclusions suggesting no greater severity of either amongst secondary dengue cases. In fact, fever duration was significantly longer amongst those with secondary compared with primary infection, potentially suggesting a greater symptomatic impact in terms of clinical infection. Additionally, whilst mean AST values were significantly higher amongst primary cases, at least two cases in the primary infection group had severe transaminitis (with AST or ALT values of >1000 U/L), suggesting that the data are skewed and that mean values are an inappropriate measure to compare. Indeed, when the proportion of patients with an AST or ALT above the upper limit of normal was examined, this did not differ significantly between groups, although the case numbers were small.

Second, the low baseline seroprevalence of dengue antibodies amongst travellers from non-endemic areas means that primary dengue cases will vastly outnumber secondary cases in this population.[9] Assuming ~5% of travellers to dengue-endemic areas have a history of past dengue exposure,[9] for every 1000 dengue cases, we would anticipate 950 primary and 50 secondary cases. Assuming a 3% risk of severe dengue in secondary cases[1] and a 2.26-fold lower risk[2] of severe dengue in primary cases (1.3%), we would expect to see 12 cases of severe dengue amongst primary cases (1.3% of 950) compared to 1.5 cases of severe dengue amongst secondary cases (3% of 50). It is therefore no surprise that a greater number of severe dengue infections were observed amongst travellers with primary dengue in the study.

Third, the study was underpowered to detect differences in rates of severe dengue between those with primary versus secondary infection. Severe dengue was observed in 4/210 primary dengue cases (1.9%); if severe infection occurred at the same rate amongst secondary cases, there would need to have been at least 52 secondary cases included in the cohort for detection of a single case of severe dengue amongst the latter group. Even if we assume a 2.26 times greater incidence of severe dengue in secondary infections (consistent with the literature),[2] the size of the secondary case cohort (35 cases) is too small to draw any meaningful conclusions regarding the frequency of severe dengue in primary compared with secondary cases from this retrospective study.

There are also other potential biases. Differentiating primary versus secondary dengue using serology or NS1 antigen testing is not straightforward, with potential for misclassification.[10] The IgG/IgM ratio threshold used (≥1.3) differs from that identified by a previous study as the optimal cut-off value to differentiate primary and secondary dengue (≥1.1).[11] Additionally, only 58% of the reported cases for the study period were included, with potential for selection bias.

Despite these limitations, the study does offer a number of valuable insights. It reassures us that severe dengue is uncommon amongst travellers presenting with symptomatic dengue, corroborating findings from a recent GeoSentinel analysis that identified complicated dengue (severe dengue or dengue with warning signs) in only 95 of 5958 dengue cases in travellers (2%).[4] The study also reaffirms that secondary cases do not usually result in severe dengue, and that there is a potential risk of severe infection amongst travellers with primary dengue infection. This underscores the importance of healthcare providers being aware that primary infections can pose risks, and reinforces the need for thorough traveller education on dengue prevention.

Future studies of dengue in non-endemic travellers will hopefully help to unravel the complex intersecting issues of prior exposure, age, and immunity on the risks of severe infection amongst primary versus secondary cases. This has increasing clinical importance given the rising global incidence and geographical range of dengue and is also important for determining priority recipients of dengue vaccines as new options emerge for pre-travel vaccination.

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Data sharing is not applicable to this article as no new data were created or analysed in this study.

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