Safety of Dengue Vaccine?

To the Editor—We acknowledge Dr de Silva's letter [1] on the profile of Takeda's dengue vaccine (TAK-003). Respectfully, we disagree with the author's assertion that the safety conclusion is inaccurate. Moreover, his assertion that TAK-003–induced immunogenicity is mainly mediated by dengue virus (DENV) serotype 2 (DENV-2) is misleading and does not reflect data from 2 large trials, demonstrating tetravalent neutralizing antibody (nAb) responses that persist for multiple years [2, 3]. Furthermore, experiments performed after anti–DENV-2 nAb depletion indicate that nAb responses to the other 3 serotypes comprise both type-specific and cross-reactive nAbs [4].

The opinion expressed by de Silva that TAK-003 shouldn't be used in seronegative populations [1] does not accurately reflect available data, given that the vaccine had 54.3% efficacy against symptomatic and 77.1% efficacy against hospitalized dengue cases in that population over 39 months [3]. The remaining 18 months of trial data, now available, further confirm the vaccine's favorable profile, with corresponding efficacy of 53.5% and 79.3% over 57 months [5]. These latest data were presented in June 2022 at Northern European Conference on Travel Medicine and Asia Dengue Summit, and a manuscript is under peer review. The overall long-term safety profile of TAK-003 is illustrated by the cumulative incidence curves (Figure 1), which emphasize its highly promising public health impact.

Importantly, dengue serotype distribution in the placebo seronegative group shows that DENV-1 was the predominant serotype over 57 months (50.6%), whereas the DENV-2 proportion was only 39.9% and 37.2% through 39 and 57 months, respectively. Therefore, the efficacy was not dependent on DENV-2 alone. Importantly, DENV-1 and DENV-2 are the 2 most common serotypes globally according to decades of dengue epidemiology [6, 7].

DENV-3 data from seronegative populations are complex, involving several confounding factors (eg, few case counts, different hospitalization practices, 2:1 randomization) and have been discussed in detail by Rivera et al [3]. Notably,

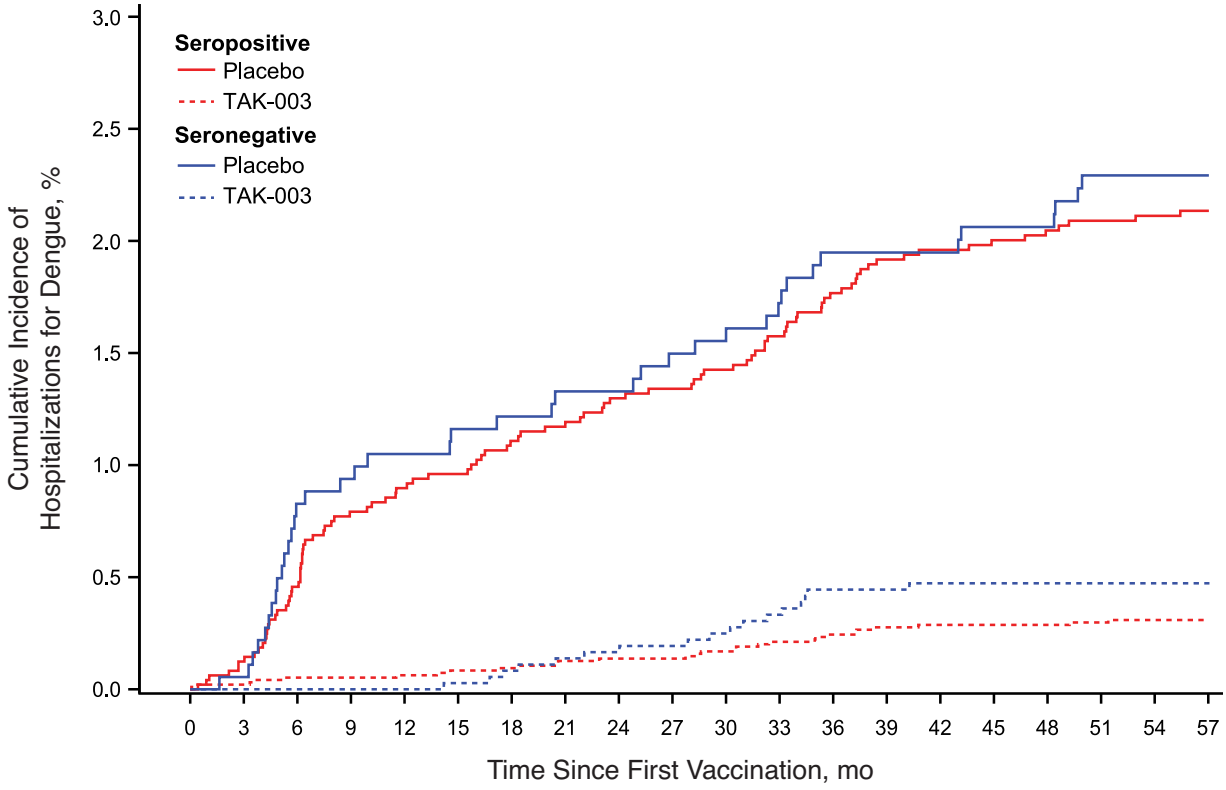

Figure 1. Cumulative incidence of hospitalization for dengue fever, by baseline serostatus in the pivotal TAK-003 vaccine efficacy trial over 57 months.

within the placebo group (all serotypes and over 39 months), the dengue hospitalization rate at Sri Lankan sites was 68%, compared with 14.4% (range, 2.5%–37.7%) in 7 other trial countries—a considerable difference that cannot be explained by case severity alone. More plausibly, it reflects the local practice of proactive hospitalization for monitoring. Importantly, none of these DENV-3 cases in Sri Lanka was severe or dengue hemorrhagic fever grade III/IV. The totality of data did not indicate a higher risk in vaccinees. Likewise, the few DENV-4 cases in seronegative participants, while reflecting low incidence according to known epidemiology, did not indicate a higher risk of severe disease in vaccinees. Although there is no important identified safety risk, thorough monitoring will continue in the postapproval period.

In summary, the TAK-003 dengue vaccine, with a dengue backbone and components of all 4 serotypes, elicits a tetravalent immune response and has demonstrated long-term safety and efficacy regardless of serostatus in a well-designed trial conducted in 8 countries over 57 months. Given the growing burden of dengue, the lack of an efficacious vaccine that can be administered regardless of preexposure status, and the well-known challenges of dengue vaccine development, an all-or-none approach is not in the interest of public health. TAK-003's profile eliminates the need for a prevaccination screening, and the vaccine can meaningfully complement the current multimodal dengue control efforts.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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A Shorter Time to Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS): Redefining Beta-Lactam–Associated DRESS

To the Editor—Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe cutaneous adverse reaction (SCAR) that can occur with medication exposure, including antibiotics [1]. DRESS is characterized by diffuse rash, eosinophilia, and organ dysfunction. However, clinical presentation can be heterogenous [2], making standardized diagnostic criteria proposed by the RegiSCAR group critical to identification of DRESS [3]. Presentation is typically delayed with traditional teaching, suggesting symptom onset occurs 2–6 weeks following medication exposure [4]. Recent studies suggest a potentially shorter drug latency with antibiotic-associated DRESS [5]. However, the latency of confirmed beta-lactam DRESS in direct comparison with other antibiotic groups remains unknown.

Using 2 previously published prospective multicenter cohorts of antibiotic hypersensitivity–tested patients from Melbourne, Australia, we identified patients with antibiotic-associated DRESS between April 2015 and June 2022 and compared patients with beta-lactam DRESS and vancomycin DRESS [6–8]. Adult (aged ≥18 years) patients who reported beta-lactam or vancomycin-associated DRESS, had a RegiSCAR score [3] of >2 (possible, probable, or definite DRESS), and had positive testing to the implicated antibiotic via a previously published ex vivo T-cell assay (enzyme-linked immunosorbent spot) or skin testing (ST; intradermal or patch test using previously deployed nonirritant concentrations of antibiotic) [7] were included. Patients with vancomycin DRESS also underwent human leukocyte antigen (HLA) typing for HLA-A*32:01, a known pharmacogenomic association [9]. DRESS patients positive to both vancomycin and a beta-lactam on any testing were excluded. Drug latency was defined as time from drug commencement until onset of DRESS. One sample Wilcoxon signed rank test was used to compare latency of beta-lactam DRESS with reported latency of 14 days, while linear regression was used for comparison with vancomycin latency.

Of 115 patients with possible DRESS (RegiSCAR >2), 68 had suspected beta-lactam–associated DRESS (41 penicillin, 27 other beta-lactam) with 12 being ST-positive. Of 41 with suspected vancomycin-associated DRESS, 17 were ST-positive with confirmed HLA