Reply to de Silva and White

To the Editor—We acknowledge the correspondence by Dr de Silva on the publication titled "Specificity and Breadth of the Neutralizing Antibody Response to a Live-Attenuated Tetravalent Dengue Vaccine," by DeMaso et al [1]. We respectfully disagree with his comments on the methods employed, the soundness of the analysis, and the conclusions.

Dr de Silva's assertion that TAK-003–induced immunogenicity is solely dengue virus-2 (DENV-2) mediated is misleading and does not reflect data from 2 large trials demonstrating tetravalent neutralizing antibody responses, which persist for multiple years [2, 3]. In children seronegative for DENV prior to vaccination, TAK-003 vaccination prevented 54.3% symptomatic and 77.1% hospitalized dengue cases over 39 months [4]. The remaining 18 months of trial data, now available, further confirm the vaccine's favorable profile with corresponding overall efficacy of 53.5% and 79.3% over 57 months [5].

Type-specific antibodies elicited by TAK-003 have been characterized in 3 studies [1, 6, 7]. Swanstrom et al demonstrated type-specific antibodies against DENV-1, DENV-2, and DENV-3. DENV-4 was not investigated due to lack of specific reagents [6]. In White et al, the frequency of DENV-2 type-specific antibodies was higher than type-specific antibodies to the other 3 DENV serotypes [7]. In DeMaso et al, type-specific antibodies to DENV-1, DENV-3, and DENV-4 were detected, while DENV-2 type-specificity was not the focus of the investigation [1].

The observation of different frequencies of serotype-specific antibodies in these 3 studies is not surprising, given the differences in vaccine formulation, vaccination regimen, experimental methods, and reagents. Samples tested in Swanstrom et al and White et al were from phase 1 and 2 clinical studies that were conducted using early formulations of TAK-003 aimed at optimizing the composition of the tetravalent vaccine, the number of doses, and dose intervals [3, 6–9]. In contrast, the samples tested in DeMaso et al were from study volunteers from 2 phase 3 clinical studies who received the final formulation and regimen of TAK-003 optimized for tetravalent immunogenicity by reducing the dose of the DENV-2 component [10]. This final formulation and regimen of TAK-003 yielded high rates of tetravalent seropositivity in baseline seronegative participants in both phase 3 clinical studies [4], and V. Tricou et al 2022 submitted and under peer review. Our aim in DeMaso et al was to assess cross-reactivity and type-specificity of neutralizing antibodies in samples that reflect the high tetravalent seropositivity rates of phase 3 trials (approximately 90% in DEN-301), rather than to exactly match absolute geometric mean titers by serotype seen in the 20 000 DEN-301 trial participants [1, 11].

TAK-003 has demonstrated long-term safety and efficacy regardless of serostatus in a phase 3 trial in children and adolescents conducted in 8 countries over 57 months. These latest data were presented in June 2022 at Northern European Conference on Travel Medicine and Asia Dengue Summi congresses, and a manuscript is under peer review. In addition to the sustained tetravalent neutralizing antibody response seen in TAK-003 clinical trials, exploratory assessments have demonstrated that TAK-003 engages multiple arms of the immune system and a broad spectrum of immune responses against all 4 vaccine components [12–14]. This includes memory B cells secreting type-specific antibodies against DENV-1, DENV-2, DENV-3, and DENV-4 [15], high avidity tetravalent antidengue binding antibodies [16], and tetravalent complement-fixing antibodies (E. J. M. Nascimento et al submitted and under peer review).

Given the growing epidemiological presence of dengue, the lack of an efficacious vaccine for people living in or traveling to dengue-endemic regions, and the well-known challenges of dengue vaccine development, a vaccine that alleviates the global burden of dengue is a dire unmet clinical need. TAK-003's profile eliminates the need for prevaccination screening and can meaningfully complement the current multimodal dengue control efforts.

Notes

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