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LETTER

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Letter to the editor: Readers response to "Predicted long-term antibody persistence for a tick-borne encephalitis vaccine: results from a modeling study beyond 10 years after a booster dose following different primary vaccination schedules"

Farid Khan[a], Xingbin Wang[a], Bing Cai[a], Wilhelm Erber[b], and Heinz-J Schmitt[c]

[a]Pfizer Vaccines, Collegeville, PA, USA; [b]Pfizer Vaccines, Vienna, Austria; [c]Pfizer Vaccines, Berlin, Germany

Dear Dr. Ellis,

We read the article by Costantini et al. titled "Predicted long-term antibody persistence for a tick-borne encephalitis [TBE] vaccine: results from a modeling study beyond 10 years after a booster dose following different primary vaccine schedules"[1] with great interest and concern. The author´s conclusion that "intervals of booster doses could be increased without compromising protection against TBE," warrants considerable scrutiny based on the data presented given the potential for unnecessary harm to patients.

The article describes the use of power-law models (PLMs) to predict the antibody levels of subjects up to 20 y after receiving the first booster dose after completion of the primary series for the inactivated whole-virus TBEV vaccine licensed as *Encepur*. The data utilized by the authors were sourced from a 3-study series that measured neutralizing antibody titers (NT) after the primary series and then 5 and 10 y post-booster dose.[2–4] However, of the 398 subjects in the initial study,[2] only less than half (191, 48%) completed all 10 y of the follow-up,[4] whereas the models presented in the study pooled all data points, regardless of follow-up available. This is apparent in Figure 2 where it appears subjects with low titers (<10) in the first 5 y post-booster dose may have been lost to follow-up in the subsequent 5 y. Without censoring the data appropriately, forecasts would overestimate persistence as the opportunity to observe antibody decay equally across subjects had not been allowed.

Further, the power-law models did not account for aging and its effect on antibody decay over time. The authors acknowledged that stratifying the models by age groups could not be done due to the limited sample size; however, immunosenescence is a critical factor as numerous studies having demonstrated depreciated baseline titers and accelerated decay with aging.[5–7] The studies that were the basis of the rationale for use of the PLMs were based on a relatively homogenous group of healthy women between 15 and 25 y old[8,9] where antibody decay due to aging would be minimal and thus would have limited impact if excluded from such a forecast. In contrast, it is an inappropriate assumption for the sample examined here where approximately 30% of participants were ≥50 y old at enrollment.

To illustrate the importance of factoring in immunosenescence, we simulated data that mimicked the published outputs utilizing a total of 600 subjects (480 [80%] <60 y old, 120 [20%] ≥60 y old) with each subject having 10 initial antibody titer measurements from 1 to 10 y post-booster dose (Figure 1). The simulated data were used to fit a non-linear PLM that included a constraint for immunosenescence (Supplementary Text 1) using SAS 9.4 software (Supplementary Text 2). Subsequently, this fitted model was then used to predict antibody titers over 20 y of post-booster dose periods (Figure 2). When stratified by age groups, the results of the simulation demonstrate that the antibody titers in the older age group would be overestimated if the effect of immunosenescence was not included in the analysis model. Thereby, the author´s conclusion that "intervals of booster doses could be increased without compromising protection against TBE" does not appear to be plausible in an aging population.

Finally, it is important to highlight the findings from Beck et al.,[10] as well as data from the German National Reference Center, that Encepur may not provide adequate protection against wild-type TBEV strains due to a mutation of its K23 seed virus utilized for production. Given this potential for reduced protection, it is even more imperative to not rely on a model (notably of limited sample that is not tuned to reflect the dynamics of an aging population) to inform on vaccination policy.

Disclosure of potential conflicts of interest

All authors are full-time employees of Pfizer Vaccines and may own stock/stock options.

CONTACT Farid Khan Farid.Khan2@pfizer.com Pfizer Vaccines, Collegeville, PA

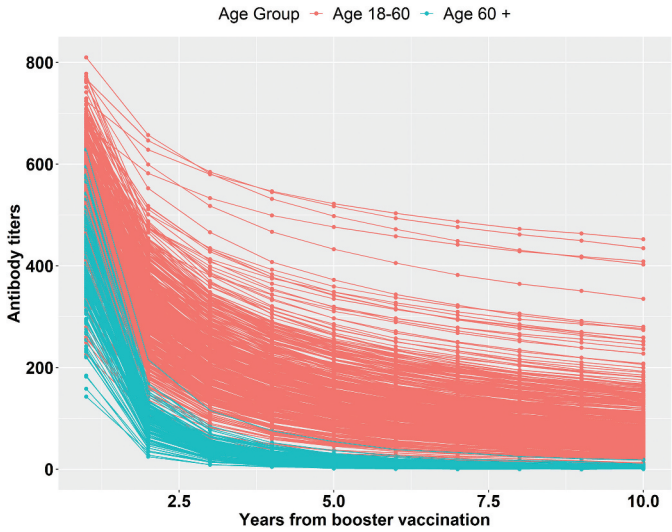

Figure 1. Antibody Titers from 1 to 10 y post-boost dose; for repeated measurements of each subject as connected through line segments.

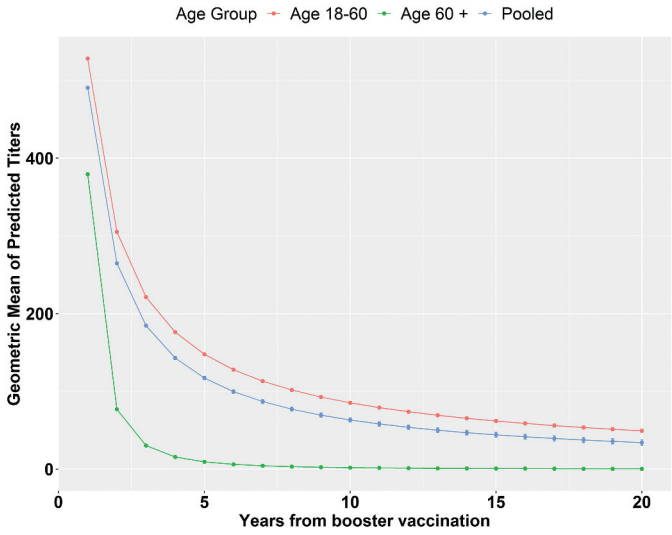

Figure 2. Predicted Geometric Mean Titers up to 20 y post-booster dose using fitted model accounting/without accounting for immunosenescence. The red and green lines show the stratified predicted values for the young age group (18–60 y) and old age group (≥60 y), respectively, based on the model including the age effect. The blue line show the pooled predicted value based on the model without including the age effect.

ORCID

Farid Khan http://orcid.org/0000-0003-3754-555X

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