

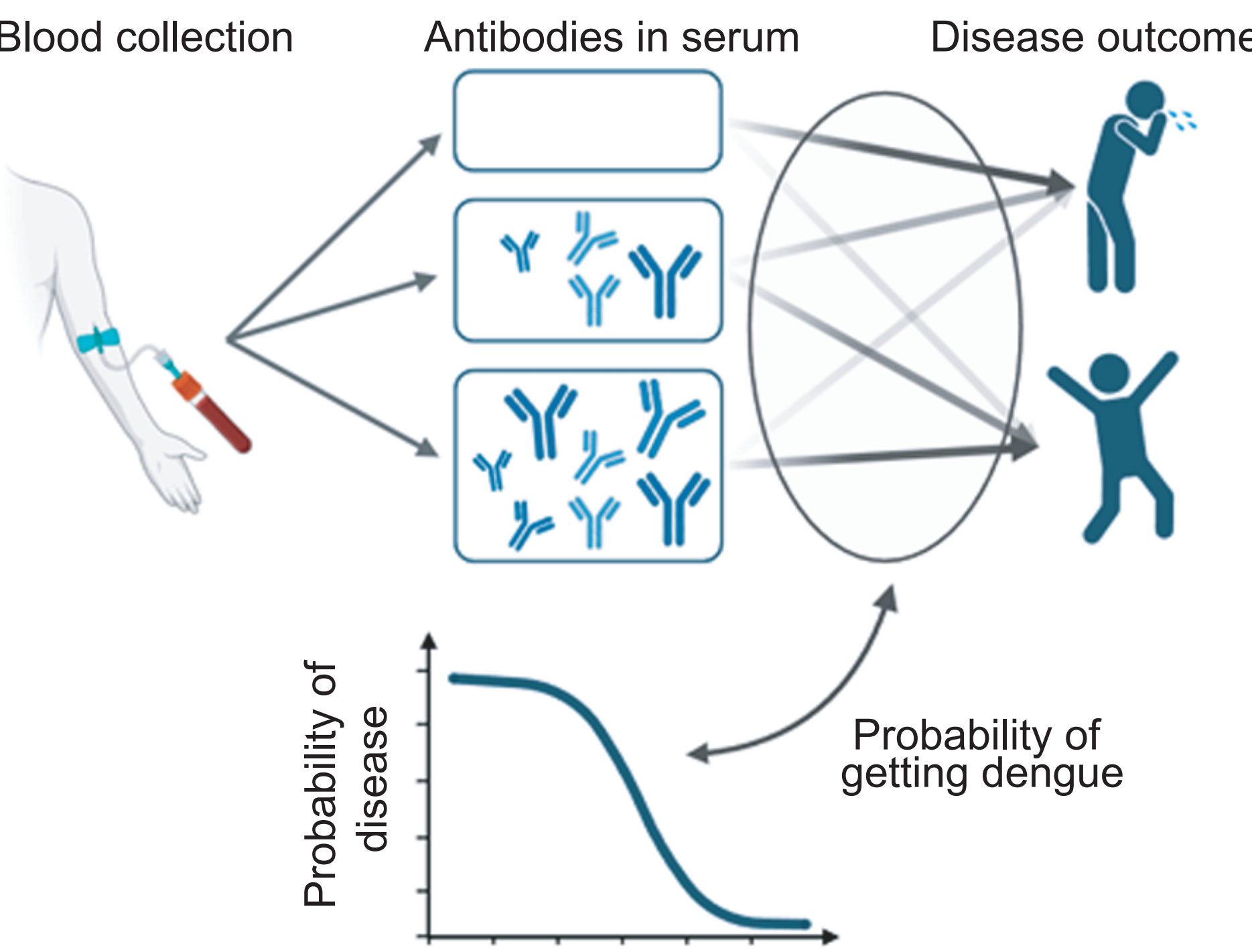
A Logistic Regression Framework for Predicting Time-Varying Vaccine Efficacy Using Longitudinal Immunogenicity Data: A Dengue Vaccine Case Study

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Abstract

- Establishing the durability of vaccine efficacy (VE) and its heterogeneity across demographic subgroups typically requires long clinical follow-up and large trials, delaying key development decisions. We present a model-based framework that leverages longitudinal immunogenicity data to predict time-varying VE within subgroups that are underpowered for traditional analyses.
- Using data from a phase 3 dengue vaccine trial, we applied a weighted pooled logistic regression linking time-dependent neutralizing antibody titers to symptomatic dengue risk. Antibody titers were identified as both a correlate of risk and protection. Immunogenicity-based VE predictions indicated sustained protection up to 2 years postvaccination in seropositive individuals, with no significant VE in seronegative individuals – consistent with findings from larger pooled efficacy studies.
- This framework enables early, subgroup-specific assessment of VE durability using routinely collected immunogenicity data, offering a scalable approach to support accelerated and more informative vaccine development.

Figure 1. Estimating individual probability of disease based on serum antibody titers for immune correlate analysis



Objectives

- Quantify the relationship between time-dependent serum neutralizing antibody titers and probability of symptomatic dengue infection
- Predict durability of vaccine efficacy** for baseline seropositive and seronegative individuals **using time-dependent antibody data**

Background

- CYD-TDV is the first vaccine approved for protection against dengue disease, caused by infection with the dengue virus (DENV)
- While there is no established absolute CoP against dengue, serotype-specific SN antibodies appear to be predictive (relative CoP) of serotype-specific dengue¹⁻⁵
- Efficacy of CYD-TDV previously shown to be declining over time and to be affected by baseline serostatus⁶⁻⁹
- We analyzed data from the longitudinal immunogenicity substudy of a phase 3 clinical trial of the dengue vaccine CYD-TDV (n = 611; >6 years of follow-up)¹⁰, focusing on serotype 2 (DENV-2), the most prevalent serotype (N = 40 DENV-2 cases, compared to 15 or fewer for other serotypes)

References

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Methods

Probability of disease, p , for individual i and time interval t

$$p_{it} = \frac{1}{1 + e^{-y_{it}}}$$

where the log-odds of disease can be estimated using linear or nonlinear effect of time-dependent antibody titer T_{it} , eg, $y_{it} = \beta_0 + \beta_1 T_{it}$ or $y_{it} = \beta_0 + \beta_1 T_{it} + \beta_2 T_{it}^2$

- Use weighted person-period data to approximate a discrete-time hazard
- Adjust for clinically relevant covariates
- Test the conditional independence of vaccination status

Immunogenicity-based prediction of time-varying vaccine efficacy

$$VE_t = (1 - \frac{p_t^{\text{vaccinated}}}{p_t^{\text{control}}}),$$

where $p_t^{\text{vaccinated}}$, p_t^{control} are expected probabilities of disease at time t , for each of the 2 populations

- Time-dependent immunogenicity data in vaccinated and control groups provide time-varying efficacy estimates
- Yearly measurements of antibodies predict yearly VE using last observation carried forward

Results

Figure 2. Time-dependent antibody titer is a CoR and CoP for DENV-2

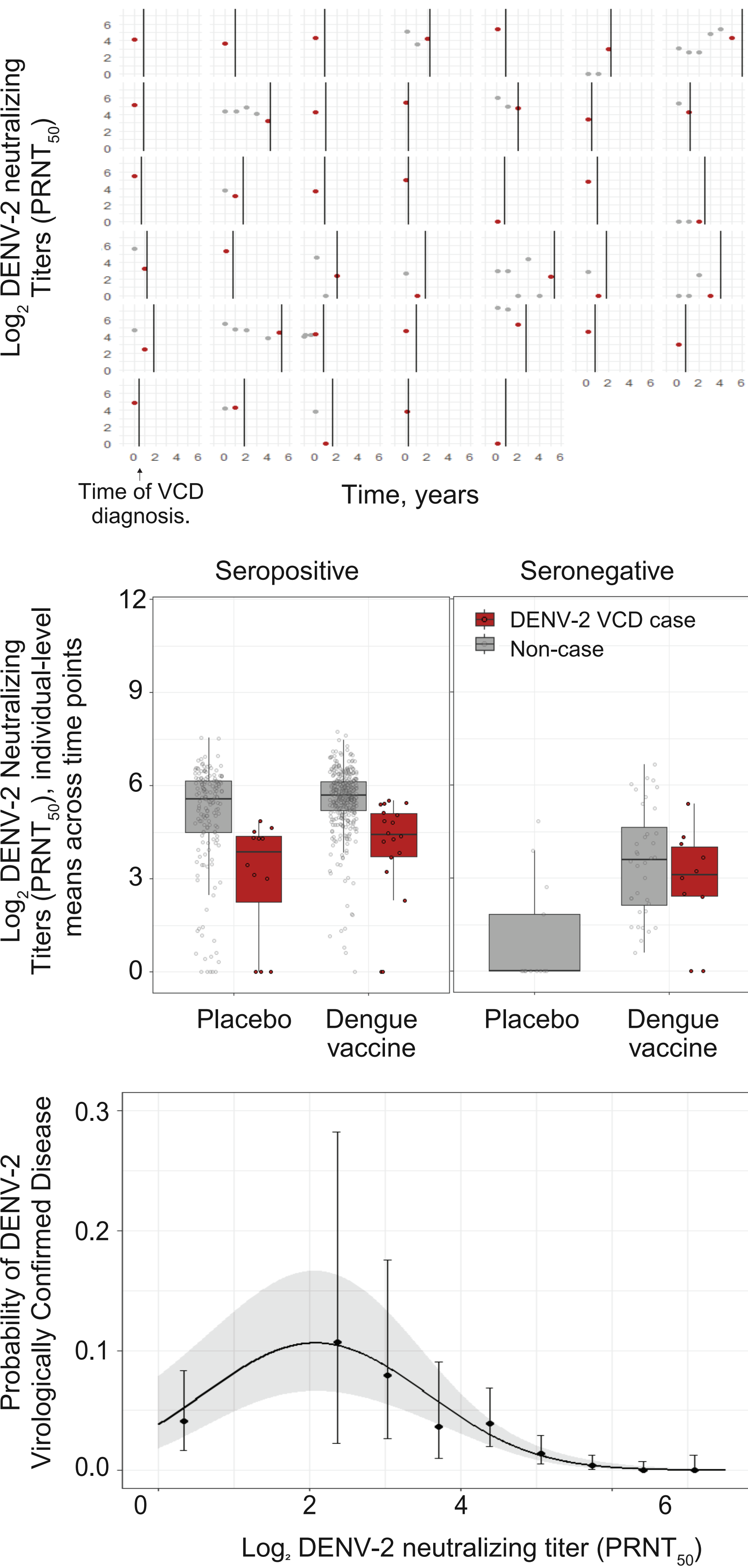
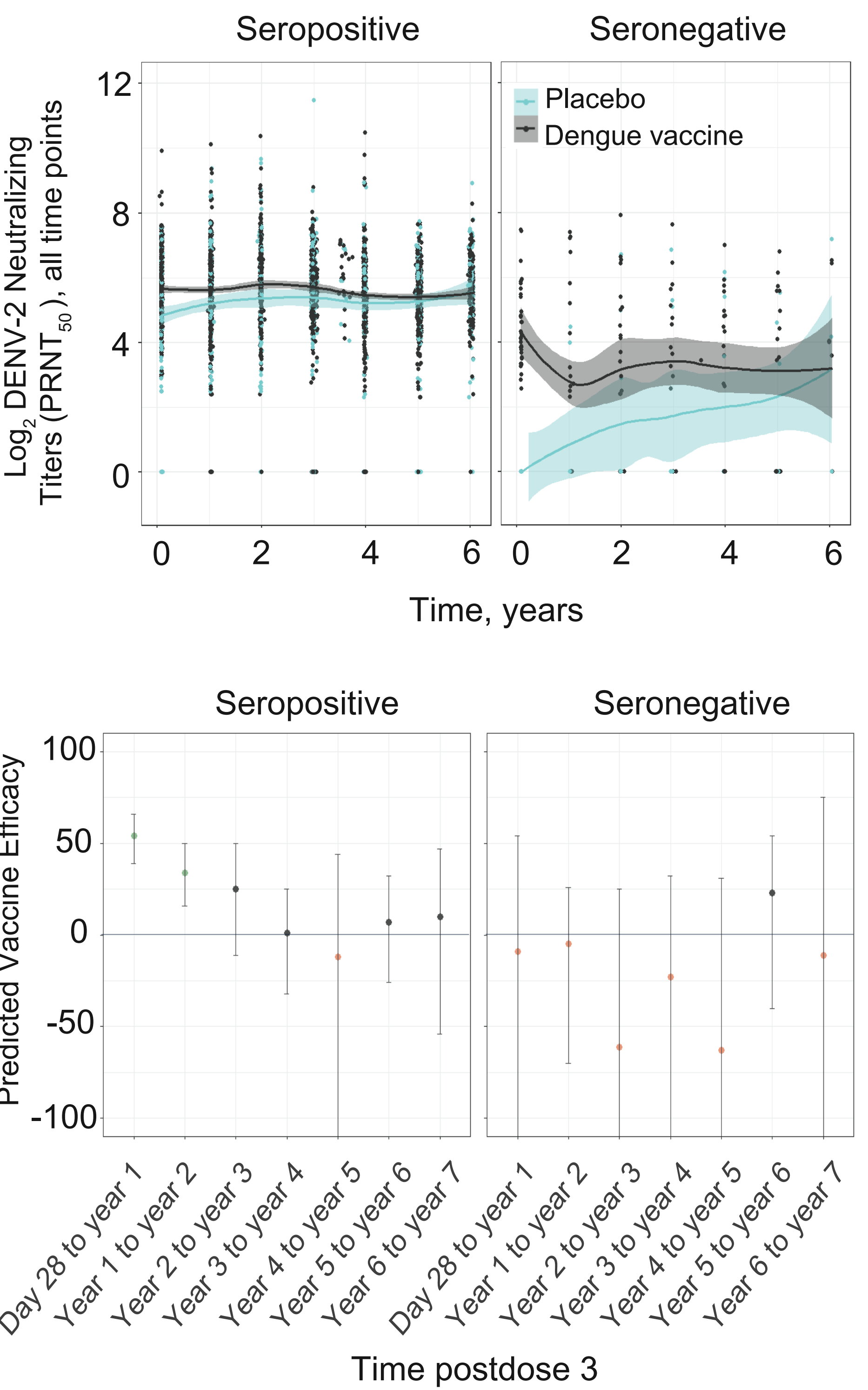


Figure 3. CYD-TDV vaccine-induced protection against DENV-2 in the seropositive group is predicted to persist up to Year 2 post vaccination



These predictions align with findings based on pooled data of 2 phase 3 trials (n = 31,125) and further support the reported impact of serostatus on CYD-TDV VE¹¹ as well as the ability of pre-exposure serotype-specific neutralizing antibodies to reliably predict protection against serotype-specific symptomatic dengue⁴.

Conclusions

Utilizing yearly immunogenicity data with a weighted cross-sectionally pooled logistic regression improves VE estimates within demographic subgroups and provides early insights into the durability of vaccine-induced protection, facilitating accelerated vaccine development for robust, long-lasting efficacy.